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SHAMBHUNATH INSTITUTE OF PHARMACY

Subject Code : RPH-843(B) Subject :Good Manufacturing Practices

SOLUTION TO THE PAPER

B.Pharm. 8th SEMESTER

FIRST SESSIONAL EXAMINATION, EVEN SEMESTER, (2019-2020)

Time –1hr 30 min **Maximum Marks – 30**

SECTION – A

1. Attempt all questions in brief. **(1*5 = 5)**

Q. No.	QUESTION	Marks	CO	BL
a.	Define Validation. Ans. Validation is a systematic approach to gathering and analyzing sufficient data which will give reasonable assurance (documented evidence), based upon scientific judgment, that a process, when operating within specified parameters, will consistently produce results within predetermined specifications.	1	2	1
b.	The rooms in manufacturing section have …….air pressure to prevent cross contamination. Ans. differential	1	1	1
c.	State the full form of O.E.C.D. Ans. Organization for Economic Cooperation & Development	1	1	1
d.	What is the importance of protocol in pharmaceutical industry. Ans. They provide a documented procedure for conducting the activities in manufacturing and thus ensure the production of products with appropriate quality.	1	1	2
e.	Define S.O.P. Ans. A Standard Operating Procedure (SOP) is a set of written instructions that document a routine or repetitive activity followed by an organization.	1	2	1

SECTION - B

2. Attempt any TWO of the following. **(2*5 = 10)**

Q. No.	QUESTION	Marks	CO	BL
a.	Explain the main concepts of GLP. Ans. **THE FUNDAMENTAL POINTS OF GLP** The GLP regulations set out the rules for good practice and help researchers perform their work in compliance with their own pre-established plans and standardized procedures. The regulations are not concerned with the scientific or technical content of the research programmes. Nor do they aim to evaluate the scientific value of the studies. All GLP texts, irrespective of their origin, stress the importance on the following points five points: **1. Resources: organization, personnel, facilities and equipment** **2. Characterization: test items and test systems**	5	1	2

3. Rules: study plans (or protocols) and written procedures
4. Results: raw data, final report and archives
5. Quality Assurance.

1. **Resources Organization and personnel**

GLP regulations require that the structure of R&D organizations and the responsibilities of R&D personnel be clearly defined. GLP also stresses that there should be sufficient staff to perform the tasks required. The qualifications and the training of staff must also be defined and documented. Facilities and equipment The regulations emphasize the need for sufficient facilities and equipment to perform the studies. All equipment must be in working order. To ensure this, a strict programme of qualification, calibration and maintenance must be adopted.

2. Characterization

In order to perform a study correctly, it is essential to know as much as possible about the materials used during the study. For studies that evaluate the properties of pharmaceutical compounds during non-clinical studies, it is a prerequisite to have details about the test item and the test system (often an animal or plant) to which the test item is to be administered.

3.Protocols and written procedures

The main steps of research studies are prescribed in the study plan or protocol. Being able to repeat studies and obtain similar results is a sine qua non of mutual acceptance of data and, indeed, a central tenet of the scientific method, so the details of routine procedures must also be available to scientists involved in the study. However, the protocol, which provides the experimental design and timeframe for the study, does not contain all the technical detail necessary to conduct the study. These details are found in written standard operating procedures (SOPs). With the protocol and the SOPs it should be possible to repeat the study exactly, if necessary.

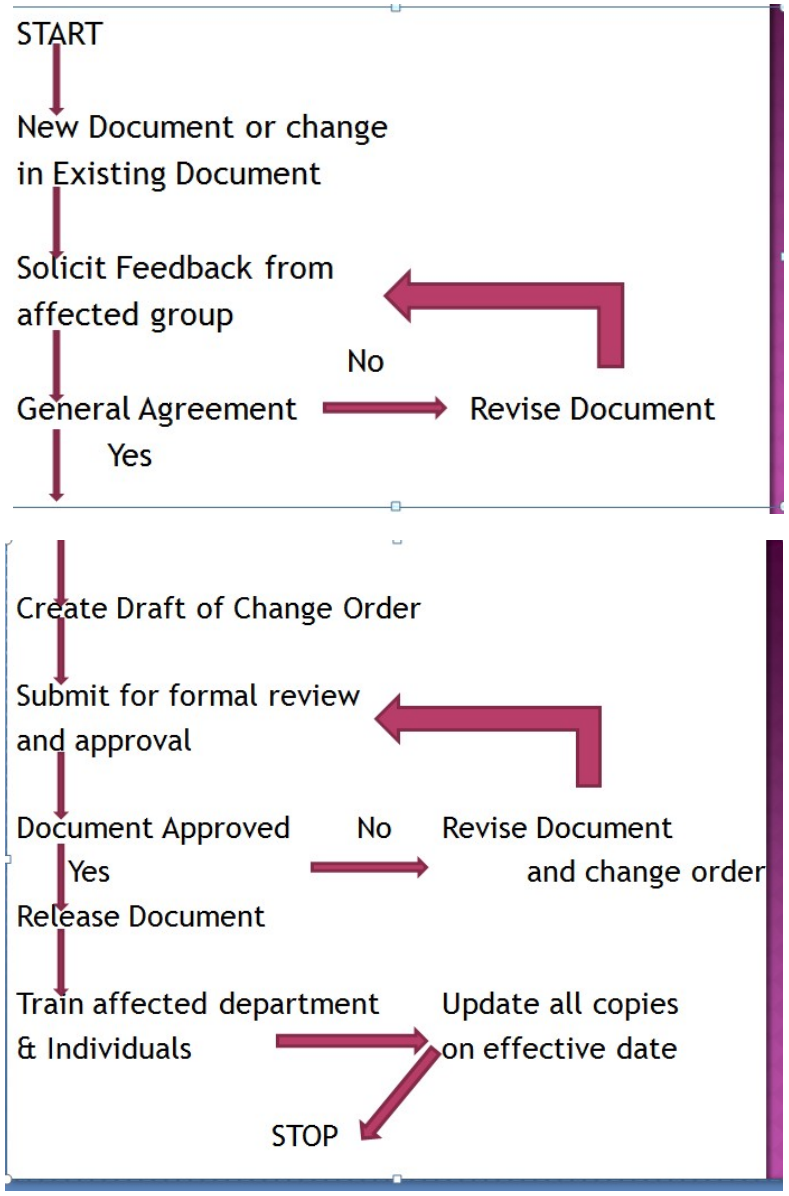
4. Results

Raw data All studies generate raw data. These are the outcome of research and form the basis for establishing scientific interpretations and arriving at conclusions. The raw data must also reflect the procedures and conditions of the study. Final Report The study report contains an account of the way in which the study was performed, incorporates the study results and includes the scientific interpretation of the data. The report is provided to regulatory authorities as part of the submission for registration and marketing approval. Archives Storage of records must ensure safekeeping for many years and allow for prompt retrieval.

5. Quality Assurance Quality assurance (QA)

As defined by GLP, is a team of persons (often called the Quality assurance unit – QAU) charged with assuring management that GLP compliance has been attained within the laboratory. QA must be independent from scientists involved in the operational aspects of the study being performed. QA functions as a witness to the whole non-clinical research process.

	Write a note on the Requirement of Location, Surrounding, Building and Premises for a Manufacturing unit. Ans. 1. GENERAL REQUIREMENTS 1.1. Location and surroundings.- The factory building(s) for manufacture of drugs shall be so situated and shall have such measures as to avoid risk of contamination from external environmental including open sewage, drain, public lavatory or any factory which product disagreeable or obnoxious odour, fumes, excessive soot, dust, smoke, chemical or biological emissions. 1.2. Building and premises.- The building(s) used for the factory shall be designed, constructed, adapted and maintained to suit the manufacturing operations so as to permit production of drugs under hygienic conditions. They shall conform to the conditions laid down in the Factories Act, 1948 (63 of 1948) the premises used for manufacturing, processing, warehousing, packaging labeling and testing purposes shall be (i) compatible with other drug manufacturing operations that may be carried out in the same or adjacent area / section; (ii) adequately provided with working space to allow orderly and logical placement of equipment, materials and movement of personnel so as to: (a) avoid the risk of mix-up between different categories of drugs or with raw materials, intermediates and in-process material; (b) avoid the possibilities of contamination and cross- contamination by providing suitable mechanism; (iii) designed / constructed / maintained to prevent entry of insects, pests, birds, vermins, and rodents. Interior surface (walls, floors and ceilings) shall be smooth and free from cracks, and permit easy cleaning, painting and disinfection; (iv) air-conditioned, where prescribed for the operations and dosage froms under production. The production and dispensing areas shall be well lighted, effectively ventilated, with air control facilities and may have proper Air Handling Units (wherever applicable) to maintain conditions including temperature and, wherever necessary, humidity, as defined for the relevant product. These conditions shall be appropriate to the category of drugs and nature of the operation. These shall also be suitable to the comforts of the personnel working with protective clothing, products handled, operations undertaken within them in relation to the external environment. These areas shall be regularly monitored for compliance with required specifications; (v) Provided with drainage system, as specified for the various categories of products, which shall be of adequate size and so designed as to prevent back flow and/or prevent insets and rodents entering the premises. Open channels shall be avoided in manufacturing areas and, where provided, these shall be shallow to facilitate cleaning and disinfection; (vi) The walls and floors of the areas where manufacture of drugs is carried out shall be free from cracks and open joints to avoid accumulation of dust. These shall be smooth, washable, covered and shall permit easy and effective cleaning and dis-infection. The interior surfaces shall not shed particles. A periodical			**1**
b.		**5**	**1**	

	record of cleaning and painting of the premises shall be maintained.			
c.	Explain in detail the process of development of S.O.P. Ans. 	**5**	**2**	**2**
d.	State the different types of validation. Ans. **Type of Validation** Retrospective Validation Prospective Validation Concurrent Validation Revalidation 1. **Retrospective Validation** Validation of a process for a product already in distribution, based on accumulated production, testing, and control dates. Summary of existing historical data. 2. **Prospective Validation**	**5**	**2**	**1**

	Validation conducted prior to distribution either of a new product, or a product made under a revised manufacturing process. Validation is completed and the results are approved prior to any product release. 3. **Concurrent Validation** A combination of retrospective and prospective validation. Performed against an approved protocol but product is released on a lot-by-lot basis. Usually used on an existing product not previously validated or insufficiently validated. 4. **Revalidation** To validate change in equipment, packaging, formulation operating procedure, or process that could impact product safety, efficacy, or potency. It is important to establish a revalidation program for critical equipment to maintain validity.			

SECTION - C

3. Attempt any ONE part of the following : (1*5 = 5)

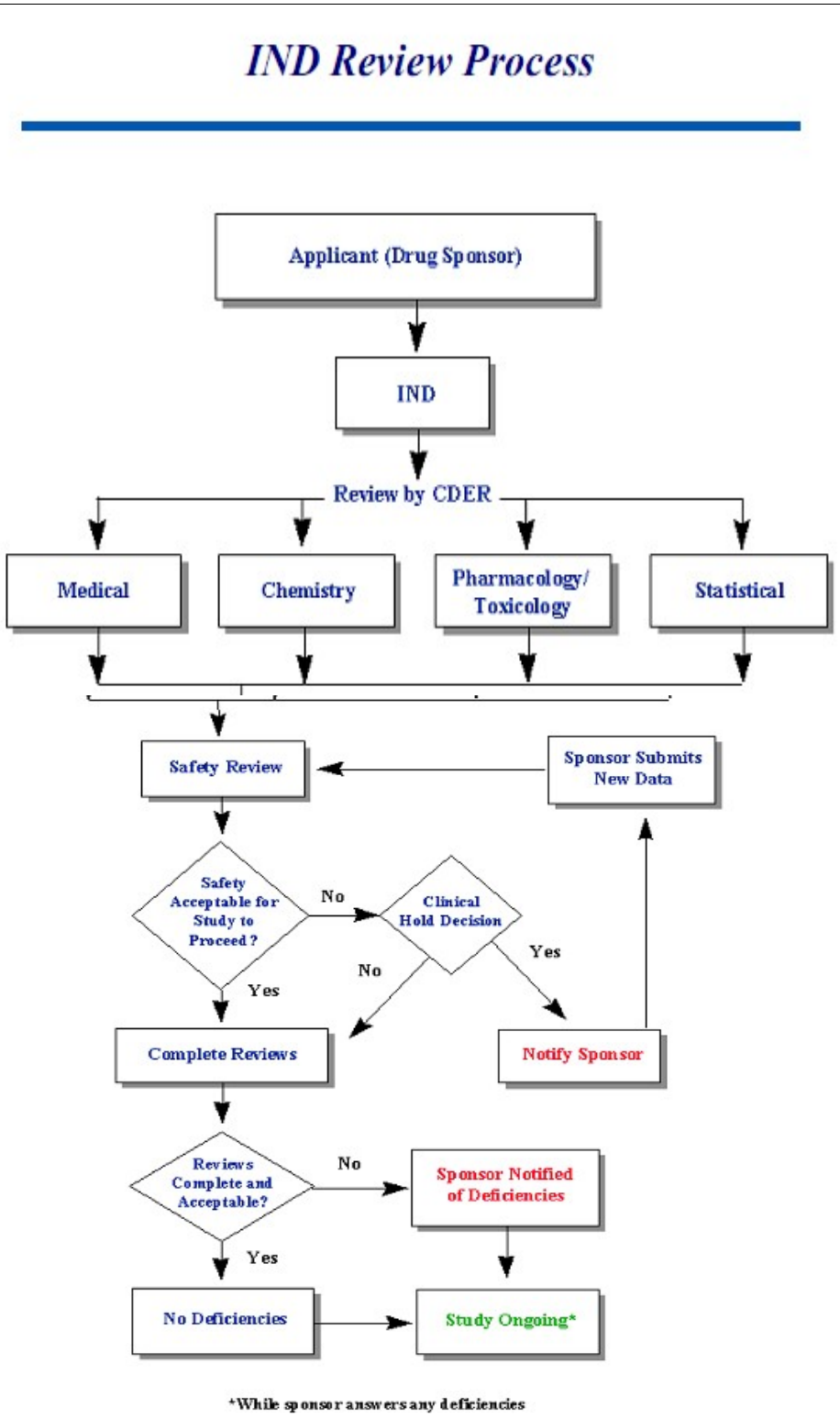
Q No.	QUESTION	Marks	CO	BL
a.	Explain in detail the principles of GCP. Ans. **GOOD CLINICAL PRACTICES** Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected; consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO). This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities. The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects. **THE PRINCIPLES OF ICH GCP** 1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s). 2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.	**5**	**1**	**2**

	3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society. 4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial. 5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol. 6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion. 7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist. 8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s). 9. Freely given informed consent should be obtained from every subject prior to clinical trial participation. 10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. 11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s). 12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol. 13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.			
b.	Give the general format of an SOP. Ans. **SOP GENERAL FORMAT** SOPs should be organized to ensure ease and efficiency in use and to be specific to the organization which develops it. There is no one "correct" format; and internal formatting will vary with each organization and with the type of SOP being written. Where possible break the information into a series of logical steps to avoid a long list. The level of detail provided in the SOP may differ based on, e.g., whether the process is critical, the frequency of that procedure being followed, the number of people who will use the SOP, and where training is not routinely available. A generalized format is discussed next.	**5**	**2**	**3**

	1 Title Page The first page or cover page of each SOP should contain the following information: a title that clearly identifies the activity or procedure, an SOP identification (ID) number, date of issue and/or revision, the name of the applicable agency, division, and/or branch to which this SOP applies, and the signatures and signature dates of those individuals who prepared and approved the SOP. Electronic signatures are acceptable for SOPs maintained on a computerized database. **2. Table of Contents** A Table of Contents may be needed for quick reference, especially if the SOP is long, for locating information and to denote changes or revisions made only to certain sections of an SOP. **3. Text Well-written SOPs** should first briefly describe the purpose of the work or process, including any regulatory information or standards that are appropriate to the SOP process, and the scope to indicate what is covered. Define any specialized or unusual terms either in a separate definition section or in the appropriate discussion section. Denote what sequential procedures should be followed, divided into significant sections; e.g., possible interferences, equipment needed, personnel qualifications, and safety considerations (preferably listed in bold to capture the attention of the user). Finally, describe next all appropriate QA and quality control (QC) activities for that procedure, and list any cited or significant references.			

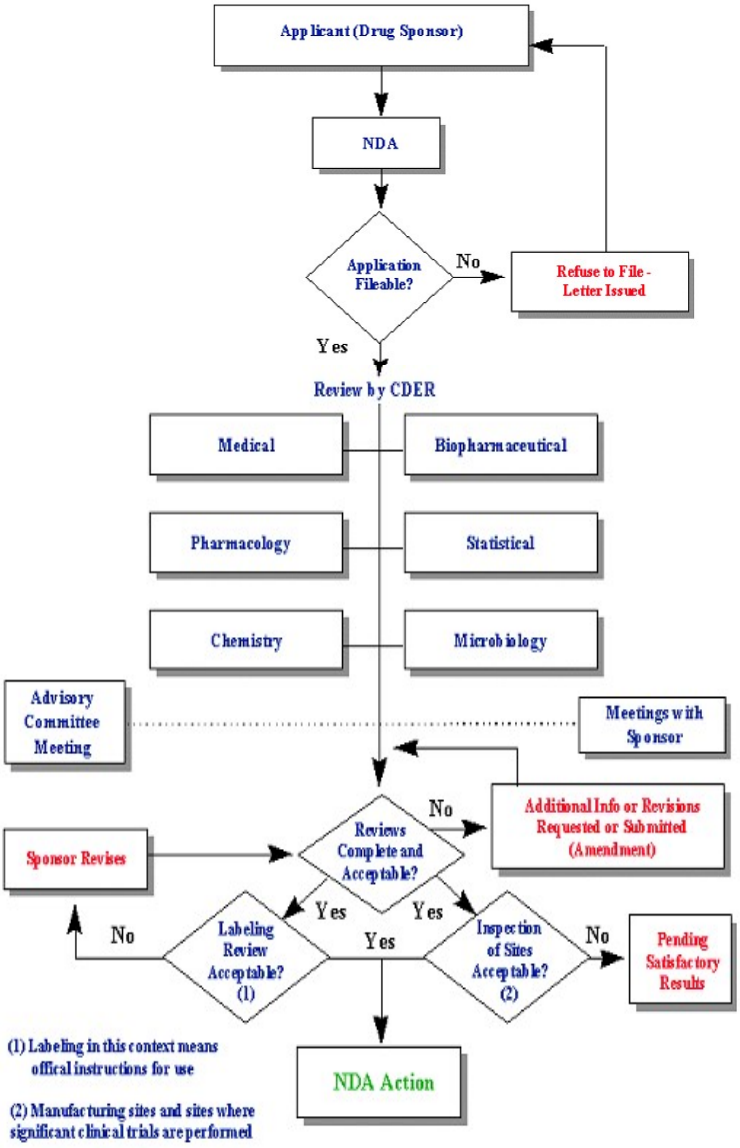
4. Attempt any ONE part of the following : **(1*5 = 5)**

Q. No.	QUESTION	Marks	CO	BL
a.	State the procedure for review of an IND. Ans.	**5**	**3**	**1**



b.	How is an NDA filed and approved. Ans.	**5**	**3**	**1**

NDA Review Process



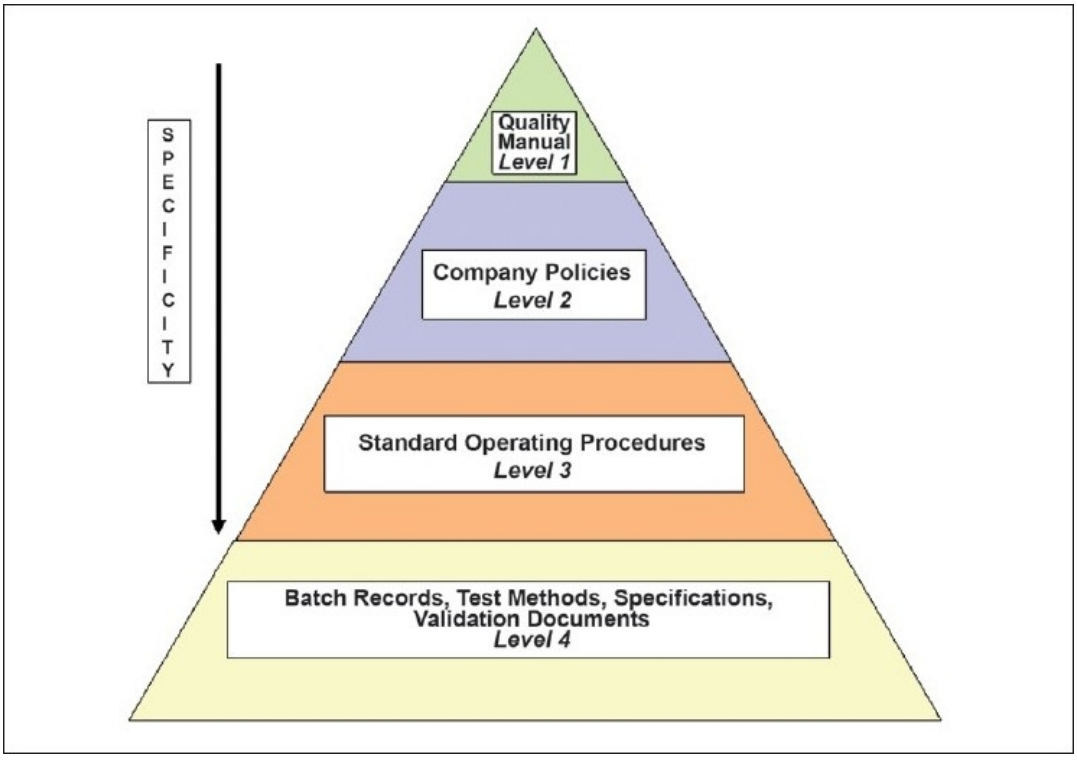
Action to be taken on an NDA:

At the conclusion of CDER's review of an application, there are three possible action letters that can be sent to the sponsor:

- Not Approvable Letter — Lists the deficiencies in the application and explains why the application cannot be approved.
- Approvable Letter — Signals that, ultimately, the drug can be approved. Lists minor deficiencies that can be corrected, often involves labeling changes, and possibly requests commitment to do post-approval studies.
- Approval Letter — States that the drug is approved. May follow an approvable letter, but can also be issued directly.

5. Attempt any ONE part of the following : **(1*5 = 5)**

Q. No.	QUESTION	Marks	CO	BL
a.	Explain the general requirements for documents in pharmaceutical industry. Ans. **General requirements** 1. Good documentation constitutes an essential part of the quality assurance system. Clearly written procedures prevent errors resulting from spoken communication, and clear documentation permits tracing of activities performed. 2. Documents must be designed, prepared, reviewed, and distributed with care. 3. Documents must be approved, signed, and dated by the appropriate competent and authorized persons. 4. Documents must have unambiguous contents. The title, nature, and purpose should be clearly stated. They must be laid out in an orderly fashion and be easy to check. Reproduced documents must be clear and legible. 5. Documents must be regularly reviewed and kept up-to-date. When a document has been revised, systems must be operated to prevent inadvertent use of superseded documents (e.g., only current documentation should be available for use). 6. Documents must not be handwritten; however, where documents require the entry of data, these entries may be made in clear legible handwriting using a suitable indelible medium (i.e., not a pencil). Sufficient space must be provided for such entries. 7. Any correction made to a document or record must be signed or initialed and dated; the correction must permit the reading of the original information. Where appropriate, the reason for the correction must be recorded. 8. Record must be kept at the time each action is taken and in such a way that all activities concerning the conduct of preclinical studies, clinical trials, and the manufacture and control of products are traceable. 9. Storage of critical records must at secure place, with access limited to authorized persons. The storage location must ensure adequate protection from loss, destruction, or falsification, and from damage due to fire, water, etc. 10. Records which are critical to regulatory compliance or to support essential business activities must be duplicated on paper, microfilm, or electronically,	**5**	**3**	**3**

	and stored in a separate, secure location in a separate building from the originals. 11. Date may be recorded by electromagnetic or photographic means, but detailed procedures relating to whatever system is adopted must be available. Accuracy of the record should be checked as per the defined procedure. If documentation is handled by electronic data processing methods, only authorized persons should be able to enter or modify data in the computer, access must be restricted by passwords or other means, and entry of critical data must be independently checked. 12. It is particularly important that during the period of retention, the data can be rendered legible within an appropriate period of time. 13. If data is modified, it must be traceable.			
b.	Write a note on Hierarchical document system. Ans. The organization should establish a hierarchical document system as mentioned in Figure 1:  **Figure 1: Hierarchical document system** 1. The regulations that a company is responsible for following (e.g., USFDA/EU GMP/ICH/Schedule M, etc.) should be at the top of the document pyramid and should govern the directives of the sublevels. 2. The level immediately beneath the regulations, level 1 document (e.g., the	**5**	**3**	**1**

Quality Manual), should break the regulations into parts specific to those that the company is required to follow. These documents should establish overall principles and guidelines for how the company plans on developing, documenting, and implementing a cGMP-compliant quality system. Top-level documents apply to all departments within a cGMP-compliant company and are not specific in nature.

3. The next level, level 2, of documents in the hierarchical document pyramid should further break down the parts of the regulations into specific subjects or topics. These documents (e.g., Company Polices) should establish guidelines with which all subordinate level procedures must comply to ensure consistency across departments.
4. Level 2 documents should not provide specific directive instructions or forms for documenting data but rather provide the overall intentions and guidelines governing critical programs or systems as well as explanation for the rationale and program designs. These documents will apply to all departments within a GMP-compliant company.
5. SOPs should be the next level in the document hierarchy after company policy documents. These types of documents should provide specific step-by-step instructions for performing the operational tasks or activities that were talked about in the previous levels (for example: SOP titled 'Writing, Revising, Numbering, and Distributing Controlled Documents'). Level 3 documents (i.e., SOPs) should be department specific or function specific.
6. The last levels of documents in a document hierarchical structure are level 4 documents. These documents are the most specific in nature, (e.g., batch record, test methods, validation procedures). They apply to a specific department, product, equipment, or process. Level 4 documents provide step-by-step instructions for production-related tasks and activities as well as provide a means for documenting such tasks using, for example, data sheets, forms, or batch records. The details outlined in these documents may override directions given in other level documents. (For example: the company's documentation SOP may state that numbers be rounded off to three significant figures; the batch record, on the other hand, may state that all numbers be expressed in scientific notation. Thus, instructions in level 4 documents, which are specific to a particular process, can overrule the

	instruction mentioned in level 3 documents, which are general in nature. The document hierarchy pyramid is one way of organizing a company's documents.			