Introduction to Various Stages in Process of Drug Development

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ABSTRACT
India is a land of diversity where alternative systems of medicine like Ayurved, Unani, Siddha practiced with equal fervor. Drug discovery is the process of identifying compounds that have the potential to become useful new therapies. Development of new drug involves two phases namely drug discovery and drug development. Internationally, India became a member of world trade organization (WTO) in 1995 & agreed to adhere to the product patent regime by 2005.

INTRODUCTION
India is a land of diversity where alternative systems of medicine like Ayurved, Unani, Siddha practiced with equal fervor. Development of new drug involves two phases namely drug discovery and drug development. Drug discovery and development is long, costly and complex process, requiring coordinated collaboration of a large number of individuals and groups from different departments including research, development, manufacturing, medical, regulatory, marketing and business management. During the development process these department interact, as appropriate, with external scientific a medical advisors, physicians, research nurses and pharmacists in order to optimize the development of new drug. It is only the successful interaction and cooperation of all these professionals that can culminate me the success full registration and marketing of a new medicine.

Drug development is considered as a series of well defined steps, culmination, if success full, in market authorization, of the drug. In practice the process is seldom linear, with many aspects of the process taking place in parallel, each step of the process from target identification through to product registration is designed to answer a specific question(s)

For an average drug, everyday of delay in obtaining marketing authorization costs approximately $300 to 350 million i.e. about 100 crore in India. In this era of pharmaceutical R & D the driving forces for therapeutic preventive and also curative.

Internationally, India became a member of world trade organization (WTO) in 1995 & agreed to adhere to the product patent regime by 2005. A well-designed and executed study has built-in provisions to ensure patient rights & safety. In fact, a patient may be far easier in a clinical trial than in routine medical care because careful observations are made in safety (toxicity) and efficacy. Historical events like sulfanilamide & thalidomide disasters are required to be avoided with appropriate clinical trials.

Two conferences were held on 10-12 October 2007 in Hyderabad on the titles discovery to innovation” & “clinical trials in India”. It had shown that how international & Indian companies are actively incorporating India as apart of a global strategy to accelerate drug discovery.

Top pharma companies like Ranbaxy, Dr. Reddy’S, Biocon, Nicholas Piramal, Wockhardt, Torrent, Avesthagen, Dabur have confirmed their R & D strategies and parntership objectives will be shared they expand their global initiatives.

Drug discovery is the process of identifying compounds that have the potential to become useful new therapies. The potential must be sufficient to justify further research and development; a company may choose to specialize in a particular therapeutic areas, on a particular approach (i.e. cancer) that will allow development of compounds across a range of disease. Larger companies are likely to adopt several or all of these approaches while a smaller one are more likely to focus specifically on one approach.
The drug discovery process

- **Methods used in drug discovery process**
  - **Screening large compounds and natural compounds** (from plants, animal products or microorganisms) for the desired activity.
  - **Changing the chemical structures of existing molecules**
    a) **Combinatorial chemistry** consists of systemically modifying an exciting compound chemically to act on a selected target. Screening of multiple compounds sometimes produce clue about how structural modification alters the action of a compound. Subsequent chemical modification of a lead compound can result in a compound with enhanced properties, such as improved absorption, enhanced safety, longer duration of action or increased efficacy. Hence, once a lead compound is developed, chemist will look to optimize the desirable characteristics of the compound.[15]
    Combinatorial Biosynthesis is a technique for modeling and building libraries of chemical compounds for consideration as drug candidates. Within these libraries, information systems are being designed to link chemical structures with various biological activities. High density synthesizers make millions of samples of the most promising compounds each year[^2].
    - **Studying disease processes**
      a) **Identification of novel pathways** that is associated with disease, selection of targets in the pathway and development of screens.
      b) **Targeted synthesis**, i.e. the creation of original molecules with biological activities that target particular stages of a disease process. Researchers design a synthesize molecules that bind to a particular locus on a target.
  - **Using computers to design new drugs**
    a) **Molecular modeling** using powerful software graphics and simulation programs to generate 3D structures of target molecules and model the affinity of different at these targets. (E.g. CoMFA, CoMSIA)
    - **Serendipity**
      Observation by chance e.g. penicillin
    - **Other new technologies**
      a) **Medical genetics**
      Genetic linkage studies are used to sift through the human genome to link genes with particular diseases while genetic association studies are used to look for known gene sequences in unselected individuals to determine whether they are more common in one disease than another.
      b) **Robotic high-throughput screening** (RHTS/HTS)
      Using miniaturization and fully automated robotic technology, compounds generated from combinatorial chemistry are tested in primary activity screens, identifying lead compounds for further biological testing and chemical optimization.

[^2]: HTS is the process of assaying a large no. of potential effectors of drug discovery by screening large libraries often composed of hundreds of thousand of compounds at a rate that may exceed 20000 compounds per week[^3].
The new drug development process

Preclinical development  clinical development

<table>
<thead>
<tr>
<th>Time Period</th>
<th>3.5-4 yrs.</th>
<th>6 yrs.</th>
<th>2.5 yrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical development</td>
<td>clinic</td>
<td>chemical synthesis</td>
<td>formulation</td>
</tr>
<tr>
<td>Phase I</td>
<td>Human pharmacology</td>
<td>Determine safety and dosage</td>
<td>Accelerated development/review</td>
</tr>
<tr>
<td>Phase II</td>
<td>Therapeutic exploratory</td>
<td>Evaluate effectiveness and look for side effects</td>
<td></td>
</tr>
<tr>
<td>Phase III</td>
<td>Therapeutic confirmatory</td>
<td>Verify effectiveness, monitor adverse reactions from long-term use</td>
<td></td>
</tr>
<tr>
<td>FDA/DCGI</td>
<td></td>
<td></td>
<td>Review process/approval</td>
</tr>
<tr>
<td>Phase IV</td>
<td>Post marketing</td>
<td></td>
<td>Additional post marketing testing required by FDA</td>
</tr>
<tr>
<td>File IND to FDA/DCGI</td>
<td>File NDA to FDA/DCGI</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5,000 compounds evaluated  5 enter trials  1 approved  SUCCESS RATE

APPLICATIONS
Investigational new drug application (IND)
After completing preclinical testing, the company files an IN with FDA to begin to test the drug in human. IND (investigational new drug application) is the means through which sponsor usually the manufactures or potential marketer obtain a legal status to call its new investigational molecule as new drug. The IND is not an application of marketing approval.

- Manufacturing information – information pertaining to the composition, manufacturer, stability and controls used for manufacturing the drug substance and the drug product, this information is assessed to ensure that the company consistently produce and supply consistent batches of the drug.
- Clinical protocols investigator information – detailed protocols for proposed clinical
studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators professionals (generally physicians) who oversee the administration of the experimental compound to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations.

- IND format

Biologics license application (BLA)
It is an alternative to FDA.\(^1\)

New Drug Application (NDA)
Following the completion of all three phases of clinical trials the company analyses all of the data & files an NDA to FDA, of the data successfully demonstrates safety & effectiveness. The NDA must contain all of the scientific information that the company has gathered. NDA is typically run 1, 00,000 pages or more. By law FDA is allowed 6 months to review an NDA in almost all cases the period between first submission of an NDA & final FDA approval exceeds that limit . The average NDA review time for new molecular entities approved in 1992 was 29.9 months.

REGULATION

CODE OF FEDERAL REGULATIONS (CFR)
The final regulations published in the federal register (daily published record of proposed rules, final rules, meeting notices, etc.) are collected in the CFR. The CFR is divided into 50 titles which represent broad areas subject to federal regulations. The FDA’s portion of the CFR interprets the federal food, drug and cosmetic act and related statues. Section 21 of the CFR contains all regulations pertaining to food and drugs. The regulations document all actions of all drugs sponsors that are required under federal law. Code of federal regulations - the final regulations published in the federal register (daily published record of proposed rules final rules, meeting notices, etc.) are collected in the CFR. The CFR is divided into 50 titles that represent broad areas subject to federal regulations. The FDA’s portion of the CFR interprets the federal food, drug and cosmetic act and related statues section 2 of the CFR contains most regulations pertaining to food and drugs. The regulations document all actions of all drug sponsors that are required under federal law\(^6\).

- The following regulations apply to the IND application process

<table>
<thead>
<tr>
<th>21 CFR Part 312</th>
<th>Investigational New Drug Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 CFR Part 314</td>
<td>IND and NDA applications for FDA approval to market a new drug</td>
</tr>
<tr>
<td>21 CFR Part 316</td>
<td>Orphan drugs</td>
</tr>
<tr>
<td>21 CFR Part 58</td>
<td>Good lab practice for nonclinical laboratory (animal) studies</td>
</tr>
<tr>
<td>21 CFR Part 50</td>
<td>Protection of human subjects</td>
</tr>
<tr>
<td>21 CFR Part 56</td>
<td>Institutional review boards</td>
</tr>
<tr>
<td>21 CFR Part 201</td>
<td>Drug labeling</td>
</tr>
<tr>
<td>21 CFR Part 54</td>
<td>Final disclosure by clinical investigators</td>
</tr>
</tbody>
</table>

REGULATORY AGENCIES
--In India, drug controller general of India (DCGI) Office under central drug standard control organization (CDSCO).
--In UK, medicines & healthcare products regulatory agency (MHRA), advised by the committee on safety of medicines (CSM).

--In USA food & drug administration (FDA).  Recommended adoption of internationally recognized ethical quality requirements are
--GCP
--Schedule Y
--Patent protection
--Abolishing the service tax

Transition in regulatory authority capabilities in India\(^{26}\)

<table>
<thead>
<tr>
<th>Before 2005</th>
<th>after 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>--Process patent law</td>
<td>--Schedule Y amended and multicentric trials</td>
</tr>
<tr>
<td>--Phase II &amp;III only</td>
<td>--Upgraded schedule M</td>
</tr>
<tr>
<td>--Phase lag</td>
<td>--CTRI funded by DST, WH &amp; ICMR</td>
</tr>
<tr>
<td></td>
<td>--GLP studies</td>
</tr>
<tr>
<td></td>
<td>--Approval by central government</td>
</tr>
<tr>
<td></td>
<td>--CDSCO-WHO pharmacovigilance programme</td>
</tr>
</tbody>
</table>
ORGANIZATION
Clinical research organization (CRO)
it is a person or organization (commercial, academic or other) contracted by the sponsor to perform one or more of a sponsor’s trial related duties and functions.
Major pharmaceutical companies estimate the total market for conducting clinical trial either directly or through CROs. CROs themselves are fast gaining importance because of global presence specialized in local expertise and competitive pricing strategies.[3]
Various CROs operating in India are:
• Clin world
• Covance mumbai diagnosearch
• Omnicare
• Pharmanet
• ICON
• Biocon clingen international22

THE CLINICAL DEVELOPMENT PLAN
Clinical research is an indispensible part of drug discovery process. The safety and toxicity data generated from pre-clinical studies enables the drug company to sagely initiate clinical trials. The scope and duration of these trials will vary widely, depending on the nature of the rug and its therapeutic application. Clinical trails con patients in the different countries are approved and monitored b different regulatory agencies like:

Physical, chemical and pharmaceutical properties and formulation
A description should be provided of the investigational product substances (including the chemical and/or structural formulae), and a brief summary should be given of the relevant physical, chemical and pharmaceutical properties. To permit appropriate safety measures to be taken in course of the trial, a description of the formulation to be used.

Non-clinical studies
The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product a metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavorable and unintended effects in humans. The information provided may include the following, as appropriate, if known/available species tested,[3]
Number and sex of animals in each group;
Unit dose (e.g., milligram/kilogram (mg/kg); dose interval)
Route of administration: duration of dosing;

Information on systemic distribution; duration of post-exposure follow-up: results, including the following aspects:
• Nature and frequency of pharmacological or toxic effects;
• Severity or intensity of pharmacological or toxic effects;
• Time to onset of effects;
• Reversibility of effects;
• Duration of effects;
• Dose response.
Tabular format/listings should be used whenever possible to enhance the clarity of the presentation. The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to; the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on mg/kg basis.

Toxicology testing
Animal pharmacology and toxicology studies – preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included if any previous experiences with the drug in humans (often foreign use).
Toxicology studies will be carried out both in vitro and on animal species known to have drug metabolism and disposition parameters (i.e. the fate of the drug in the body) resembling those in humans – although the pharmaceutical industry is always striving to replace animal experiments with meaningful in vitro studies (such as Ames test). toxicology and safety testing determine the potential risk a compound poses to man and the environment13.

Toxicity studies are done to calculate:
• Maximum tolerated dose
• Gross effects, clinical chemistries
• Gross pathology to indicate target organs
• Satisfactory therapeutic ratio vis-à-vis animal efficacy studies.

Toxicology studies in preclinical stage are conducted to
• Select or reject lead candidate
• General indication of suitability
• Dose selection and guidance to clinician.
Phases of clinical research
Clinical research is done in four phases (I, II, III, and IV), each designed to address different questions. The knowledge gained from one phase is assessed before progressing to the next phase. However, research in a particular phase may continue after the drug has progressed to further stages of development.

Based upon data gathered from the pre-clinical (animal testing) trials, the sponsor has some estimation of:
-- The drug’s therapeutic effect and dose levels.
-- Toxicity profile and dose levels.
This information is used in the design of phase I trials.

Phase I clinical trials
The first question in drug research is to find out the safety of drug in humans. Phase I studies, sometimes called “first in man”, starts to answer this question by testing the investigational product in healthy volunteers. If the drug has a potential for toxic adverse events, it may be given only to subjects with the targeted condition to reduce risks to healthy subjects (i.e. anticancer drugs are never tested in healthy volunteers). The main purpose of the initial phase I studies is to establish a safe dosage ranges. These studies are designed to determine the metabolic and pharmacologic actions to the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During phase I, sufficient information about the drug’s pharmacokinetics (ADME) and pharmacological effects should be obtained to permit the design of well controlled, scientifically valid phase II studies.

Phase I trial address
-- How rapidly the drug is adsorbed?
-- Where is the drug distributed in the body?
-- Which organs or organ system are involved in metabolism of the drug?
-- How quickly is the drug eliminated from the body?

Fact: only about 70% of experimental drugs passes phase I clinical trials
What is the minimum effective dose?
What is the maximum tolerated effective dose?
Is the drug effective in mild, moderate and severe cases of the disease or condition?
Is the drug effective for all expected indications?

Fact: only about 35% of experimental drugs pass phase II clinical trials.

Phase III clinical trials
Phase III studies are expanded, controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained in phase II, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug.

Phase III clinical trials may involve several hundred to several thousands patients and lasts 1-5 years. The aims of this phase are to verify the drug’s effectiveness and any adverse reactions in a large group of patients over a longer period of exposure, to establish safety and efficacy of drug.

Phase III studies also provide an adequate basis for extrapolation the results to the general population and transmitting that information in the package insert. Very often Phase III clinical trials involve different patients’ sub-groups such as children, the elderly and perhaps those with impairments in liver or kidney function.

In both phases II and III, regulatory bodies can impose a clinical hold if a study is unsafe (as in phase I), or if the protocol is clearly deficient in meeting its stated objectives. Great care is taken to ensure that this determination is not made in isolation, but reflects current scientific knowledge, regulatory agency experience with the design of clinical trials, and experience with the class of drugs under investigation.

Once the Phase III clinical trials have been completed satisfactorily, the drug company is in a position to apply the marketing application to the regulatory authorities to market the drug.

Phase III trial address
--Overall benefit-risk relationship
--Adverse reactions in a large group of patients over a longer period of exposure
--The ideal dosage regimen
--Should the drug is allowed to be marketed?

Fact: only about 25% of experimental drugs pass phase III clinical trials

Phase IV Clinical Trials (Post-Marketing Surveillance)
Sometimes adverse drug reaction only comes to light after the drug has been in the market for a while and has been used by very large numbers of patients. Phase IV Clinical Trials (Sometimes referred to as Post-Marketing Surveillance) identifies such Problems. Withdrawal of a drug from the market is not an uncommon occurrence – one notorious case in the 1960’s involved the drug Thalidomide. Phase IV trials are done after a drug has been shown to work and has been granted a license.

Phase IV Trial address
--More about the side effects and safety of the drug
--Long term risks and benefits of the drug
--How well the drug works when it’s used more widely than in clinical trial?

FIXED DOSE COMBINATIONS (FDCs)
Fixed Dose Combinations refer to products containing one or more active ingredients used for a particular indication(s). FDCs can be divided into the following groups and data required for approval for marketing is described below:
(a) The first group of FDCs includes those in which one or more of the active ingredients is a new drug. For such FDCs to be approved for marketing data to be submitted will be similar to data required for any new drug (including clinical trials) [see rule 122E, item (a)].

(b) (i) The second group FDCs includes those in which active ingredients already approved/marketed individually are combined for the first time, for a particular claim and where the ingredients are likely to have significant interaction of a pharmacodynamic or pharmacokinetic nature. If clinical trials have been carried out with the FDC in other countries, reports of such trials should be submitted. If the FDC is marketed abroad, the regulatory status in other countries should be stated.

(ii) For marketing permission, appropriate chemical and pharmaceutical data will be submitted. In case such a combination is not marketed anywhere in the world but these drugs are already in use concomitantly (not as an FDC but individually) for the said claim, marketing permission may be granted based on chemical and pharmaceutical data. Data showing the stability of the proposed dosage form will also have to be submitted.

(iii) For any other such FDCs, clinical trials may be required. For obtaining permission to carry out clinical trials with such FDCS a summary of available pharmacological, toxicological and clinical data on the individual ingredients should be submitted, along with the rationale for combining them in the proposed ratio. In addition, acute toxicity data (LD 50) and pharmacological data should be submitted on the individual ingredients as well as their combination in the proposed ratio.

(c) The third group of FDCs includes those which are already marketed, but in which it is proposed either to change the ratio of active ingredients or to make a new therapeutic claim. For such FDCs, the appropriate rationale including published reports (if any) should be submitted to obtain marketing permission. Permission will be granted depending upon the nature of the claim and data submitted.

(d) The fourth group of FDC includes those whose individual active ingredients (or drugs from the same class) have been widely used in a particular indication(s) for years, their concomitant use is often necessary and no claim is proposed to be made other than convenience. It will have to be demonstrated that the proposed dosage form is stable and the ingredients are unlikely to have significant interaction of a pharmacodynamic or pharmacokinetic nature. No additional animal or human data are generally required for these FDCs, and marketing permission may be granted if the FDC has an acceptable rationale.

STUDIES IN SPECIAL POPULATIONS
Information supporting the use of the drug in children, pregnant women, nursing women, elderly patients, patients with renal or other organ systems failure, and those on specific concomitant medication is required to be submitted if relevant to the clinical profile of the drug and its anticipated usage pattern. Any claim sought to be made for the drug product that is not based on data submitted under preceding items of this Schedule should be supported by studies included under this item of the Schedule

(1) Geriatrics
Geriatric patients should be included in Phase III clinical trials (and in Phase II trials, at the Sponsor’s option) in meaningful numbers, if:

- (a) The disease intended to be treated is characteristically a disease of aging; or
- (b) The population to be treated is known to include substantial numbers of geriatric patients; or
- (c) When there is specific reason to expect that conditions common in the elderly are likely to be encountered; or
- (d) When the new drug is likely to alter the geriatric patient’s response (with regard to safety or efficacy) compared with that of the non-geriatric patient.

(2) Paediatrics

(i) The timing of paediatric studies in the new drug development program will depend on the medicinal product, the type of disease being treated, safety considerations, and the efficacy and safety of available treatments. For a drug expected to be used in children, evaluations should be made in the appropriate age group. When clinical development is to include studies in children, it is usually appropriate to begin with older children before extending the trial to younger children and then infants.

(ii) If the new drug is for diseases predominantly or exclusively affecting paediatric patients, clinical trial data should be generated in the paediatric population except for initial safety and tolerability data, which will usually be obtained in adults unless such initial safety studies in adults would yield little useful information or expose them to inappropriate risk.

(iii) If the new drug is intended to treat serious or life-threatening diseases, occurring in both adults and paediatric patients, for which there are currently no or limited therapeutic options, paediatric population should be included in the clinical trials early, following assessment of initial safety data and reasonable evidence of potential benefit. In circumstances where this is not possible, lack of data should be justified in detail.
If the new drug has a potential for use in paediatric patients, paediatric studies should be conducted. These studies may be initiated at various phases of clinical development or after post marketing surveillance in adults if a safety concern exists. In cases where there is limited paediatric data at the time of submission of application - more data in paediatric patients would be expected after marketing authorisation for use in children is granted.

The paediatric studies should include:

(a) Clinical trials,
(b) Relative bioequivalence comparisons of the paediatric formulation with the adult formulation performed in adults, and
(c) Definitive pharmacokinetic studies for dose selection across the age ranges of paediatric patients in whom the drug is likely to be used. These studies should be conducted in the paediatric patient population with the disease under study.

If the new drug is a major therapeutic advance for the paediatric population - the studies should begin early in the drug development, and this data should be submitted with the new drug application.

Paediatric Subjects are legally unable to provide written informed consent, and are dependent on their parent(s)/legal guardian to assume responsibility for their participation in clinical studies. Written informed consent should be obtained from the parent/legal guardian. However, all paediatric participants should be informed to the fullest extent possible about the study in a language and in terms that they are able to understand. Where appropriate, paediatric participants should additionally assent to enrol in the study. Mature minors and adolescents should personally sign and date separately designed written assent form. Although a participant’s wish to withdraw from a study must be respected, there may be circumstances in therapeutic studies for serious or life-threatening diseases in which, in the opinion of the Investigator and parent(s)/legal guardian, the welfare of a pediatric patient would be jeopardized by his or her failing to participate in the study. In this situation, continued parental/legal guardian consent should be sufficient to allow participation in the study.

For clinical trials conducted in the paediatric population, the reviewing ethics committee should include members who are knowledgeable about pediatric, ethical, clinical and psychosocial issues.

Pregnant or nursing women

(i) Pregnant or nursing women should be included in clinical trials only when the drug is intended for use by pregnant/nursing women or foetuses/nursing infants and where the data generated from women who are not pregnant or nursing, is not suitable.

(ii) For new drugs intended for use during pregnancy, follow-up data (pertaining to a period appropriate for that drug) on the pregnancy, foetus and child will be required. Where applicable, excretion of the drug or its metabolites into human milk should be examined and the infant should be monitored for predicted pharmacological effects of the drug.

Generic drug product

A generic drug product is one that is comparable to an innovator drug product in dosage form, strengths, and route of administration, quality, performance characteristics and intended use. Since generics used the same active ingredient and are shown to work the same way in the body, they have same risks and benefits as their brand name counterparts. Generic brands are less expensive because generic manufacturers don’t have the investment costs of the drug development.

Abbreviated new drug application (ANDA)

An Abbreviated new drug application is submitted to regulatory bodies to obtain the approval to market a generic drug product. It contains data which, when provided for preview and once approved, an applicant may manufacture and market the generic drug product as a low cost alternative. Generic drug applications are termed “abbreviated” because they are generally not required to include (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent to innovator. Generic drug application reviewers’ focus on bioequivalence data, chemistry and microbiology data, plant inspection and drug labeling information.

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A registry, clinical trial registry-India (CTRI) funded jointly by DST, WHO & ICMR has been initiated. Other trial registries are ACTR, clinical trials.gov, ISCRITN etc. Also national pharmacovigilance programmes coordinated by CDSCO under the aegis of DGHS, New Delhi are there to protect our population from potential harms. 21st May is celebrated as international clinical trials day.

Appendix II

Major players in clinical trials
- Tata memorial centre
- Clinigene
- Dr.reddy’s laboratories ltd.
- GSK
- Lupin ltd.
- Novartis
- Pfizer ltd.
- Ranbaxy laboratories
- Vimta labs ltd.
- Matrix labs.
- Sanofi-aventis pharma ltd

Some useful web links of clinical trials
- www.openclinica.org
- www.clinicaltrials.gov/
- www.who.int/ictrp/
- www.lillytrials.com/
- www.strokecentre.org/trials/
- www.ctr.gsk.co.uk/
- www.ccfar.org/clinical/
- www.clinicalstudyresults.org
CONCLUSION

Although it typically takes 10-12 yrs. & millions of dollars to bring one new drug to market the success rate is small. Clinical development is complex & is highly sensitive to globally accepted quality, ICH, GCP & ethics standards. Clinical trials registry (CTRI), global clinical trial programme & foundation of knowledge based industry, very less service tax, are attracting developed countries. But in developing countries (like India) no company or institute wants to or can, invest such time & resources for marginal improvement in responses over existing therapies. Even for new molecules due to inappropriate checking at regulatory level itself, though obtain patent but due to no industrial applicability cannot be applied appropriately through IND to DCGI .Thus, there is no appropriate reason, why clinical research cannot follow in those footsteps.

REFERENCES

3. ICH topic E6, Guideline for good clinical practice, the European agency for the evaluation of medicinal products, step 5, consolidated guideline 1.5.96.
5. Gupta Manish, M-Pharm sem. II (QA) 2007-08, Seminar Report, Lachoo Memorial College of Science & Technology, Jodhpur.
12. www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/default

Appendix III

Consolidated list of FDCs (Fixed Dose Combinations) licensed by SLAs but not permitted by DCGI (20th March 2009) 24

<table>
<thead>
<tr>
<th>S.No. per DCGI list</th>
<th>Name of FDC</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td>Analgin + dextropropoxyphene</td>
<td>Analgesic</td>
</tr>
<tr>
<td>53</td>
<td>Analgin + diazepam + diphenhydramine</td>
<td>CNS</td>
</tr>
<tr>
<td>56</td>
<td>Analgin + diazepam + dicyclomine</td>
<td>GI</td>
</tr>
<tr>
<td>58</td>
<td>Analgin + ketoprofen</td>
<td>Orthopaedic</td>
</tr>
</tbody>
</table>

A total of 17 drugs were banned
12. Activated charcoal + fungal diastase + lactic acid | GI
60. Artesunate + arteether + arteether | Antimalarial

A total of 8 drugs were absorbed
1. 5-bromosalicyl-4-chloranilide + salicylic acid | Dermatological
64. Atorvastatin + acetyl salicylic acid + caffeine | Orthopaedic
227. Mecobalamine + melamine mandelate | Nutritional

A total of 18 drugs could be discontinued

Appendix IV

Some drugs under clinical trials 41

<table>
<thead>
<tr>
<th>S.no.</th>
<th>Drug</th>
<th>Phase</th>
<th>Sponsor</th>
<th>Mode of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AZD-9272</td>
<td>I</td>
<td>AstraZeneca-NPS Pharma</td>
<td>mgluR1 antagonist</td>
</tr>
<tr>
<td>2</td>
<td>BL-1020</td>
<td>I</td>
<td>Bio-line Rx</td>
<td>Dopamine antagonist with GABA modulation</td>
</tr>
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<td>3</td>
<td>Cherythrine</td>
<td>I</td>
<td>Matrinus pharma</td>
<td>PKC inhibitor</td>
</tr>
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<td>4</td>
<td>CRD-101</td>
<td>I</td>
<td>Curdium</td>
<td></td>
</tr>
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<td>5</td>
<td>GSK 189254</td>
<td>I</td>
<td>GSK</td>
<td>H3 antagonist</td>
</tr>
<tr>
<td>6</td>
<td>BX-EGF (panutumumab)</td>
<td>II</td>
<td>Abgenix</td>
<td>For growth factor receptor</td>
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<td>7</td>
<td>Prazatrexate</td>
<td>II</td>
<td>Allos therapeutics</td>
<td>Small cell lung cancer</td>
</tr>
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<td>8</td>
<td>Sitaxsentan</td>
<td>III</td>
<td>Encysive pharmaceuticals</td>
<td>Artrial hypertension</td>
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<td>Rifaxmin</td>
<td>III</td>
<td>Salix pharmaceuticals</td>
<td>Oral antibiotic</td>
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