BP702T(Industrial PharmacyII)Theory

Unit V

IndianRegulatoryRequirements

Central Drugs Standard Control Organization (CDSCO) and state licensing authority: OrganizationandResponsibilities,CertificateofPharmaceuticalProduct(COPP),Regulatory requirementsandapprovalproceduresofNewdrugs.

Abbreviations

DRA-DrugRegulatoryauthority
CDSCO-CentralDrugsStandardControlOrganization DCGI -
Drugs Controller General of India
DTAB-DrugTechnicalAdvisoryBoard
DCC- Drug Consultative CommitteeDC
Act- Drug and Cosmetic Act
FDC-FixedDoseCombinations
SEC-SubjectExpertCommittee
NDAC- New Drug Advisory Committees
SDRA- State Drug Regulatory Authorities
CDTL- Central Drugs Testing Laboratories
COPP-CertificateofPharmaceuticalProduct
QSE- Quality, safety and efficacy
GMP- Good manufacturing practices
MAH-Marketingauthorizations holders
API- Active pharmaceuticalingredients
OTC- Over the counter drug
ICH-InternationalConferenceonHarmonization

Introduction-

The drug regulatory authority (DRA) istheagency that developsandimplements most of the legislation and regulations on pharmaceuticals. Its main task is to ensure the quality, safety and efficacyofdrugs,andtheaccuracyofproductinformation.Thisisdonebymakingcertain rules that the manufacture, procurement, import, export, distribution, supply and sale of drugs, product promotion and advertising, and clinical trials are carried out according to specified standards.

FunctionsofRegulatory Authority:

- Productregistration(drugevaluationandauthorization,andmonitoringofdrug efficacy and safety.
- Regulationofdrugmanufacturing,importation,anddistribution.
- Regulation&Controlofdrugpromotionandinformation.
- Adversedrugreaction(ADR)monitoring.
- Licensingofpremises,personsandpractices.
- Maingoalofdrugregulationistoguaranteethesafety,efficacyandqualityofdrugs.

CentralDrugs StandardControl Organization (CDSCO)-

CentralDrugsStandard Control Organization(CDSCO)exercisesregulatorycontroloverthe qualityofdrugs,cosmeticsandnotifiedmedicaldevicesinthecountry.TheCDSCOofIndia ismainregulatory body forregulationofpharmaceutical,medicaldevicesandClinicalTrials.

It istheCentral Drug Authorityfor discharging functions assigned to the Central Government undertheDrugsandCosmeticsAct.ItsHeadquarterislocatedatFDABhawan,KotlaRoad, NewDelhiandfunctionsundertheDirectorateGeneralofHealthServices,ministryofhealth andfamilywelfareGovernmentofIndia.

Itisdividedintozonalofficeswhichdopre-licensingandpost-licensinginspections,post-marketsurveillance,andrecallswhenneeded.

Vision: ToProtect&PromoteHealthinIndia

Mission: Tosafeguardandenhancethepublichealthbyassuringthesafety,efficacyand qualityofdrugs,cosmeticsandmedicaldevices.

DrugsControllerGeneralof India (DCGI)

• He/sheisaresponsibleforapprovalofNewDrugs,MedicaldevicesandClinicalTrailstobe conducted in India.

• He is appointed by the central government under the DCGI the State drug control organizationwill be functioning.

• TheDCGIisadvisedbytheDrugTechnicalAdvisoryBoard(DTAB)andtheDrug Consultative Committee (DCC).

TheDCGIisresponsibleforhandlingmattersofproductapprovalandapprovalstandards, clinicaltrials,introductionofnewdrugs,andimportlicensesfornewdrugs.Adrugmaybe licensedformanufacturinginastateonlyonceithasbeenapprovedbyCDSCO.

Processof drugregulation

TheDCActentrustsCDSCOwiththeresponsibilityfortheapprovalofnewdrugs,andthe conduct of clinical trials in the country, as well as laying down the standards for drugs, controllingthequalityofimporteddrugs,oversightovertheSDRAs,andanadvisoryrolein ensuringuniformityintheenforcementoftheDCActitself.

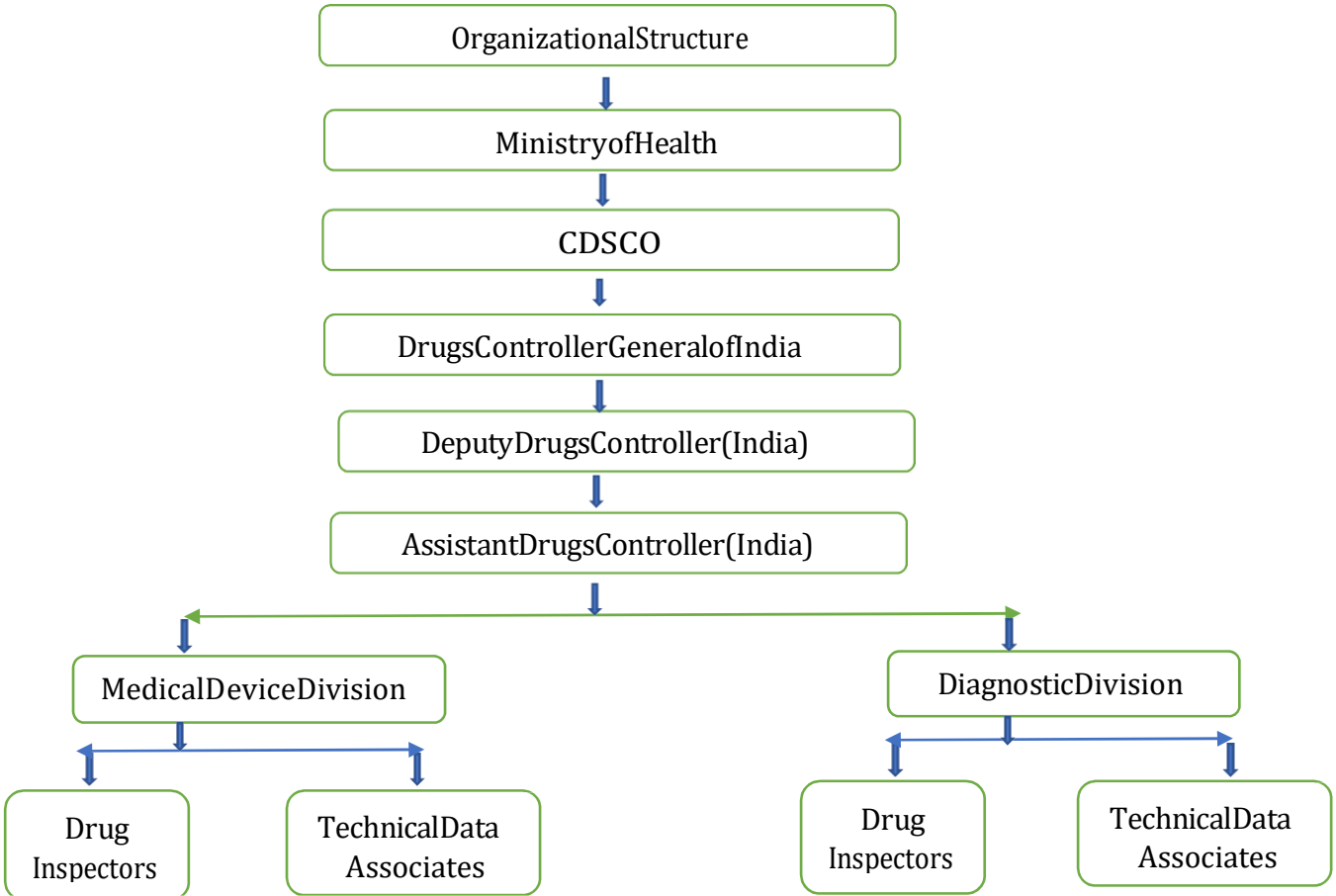
CDSCOapprovesnewdrugsbasedonacombinationofnon-clinicaldata,clinicaltrialdata (focusingonsafetyandefficacy)fromabroadaswellasinIndia,andtheregulatorystatusof thedruginothercountries.Thelawaroundnewdrugapprovalsiscontainedin Rules122A, 122B,122D,122DA,122DAA,122DAB,122DAC,122DB,122DDand122Eof Schedule-YoftheDCRules.Thelawpermitsawaiverofrequiringlocalclinicaltrialsifthe Licensing Authority decides it is in the public interest to grant permission to import / manufacture the newdrug on the basis of data available from other countries. In special circumstances, such as drugs required in life threatening / serious diseases or diseases of special relevancetotheIndianhealthscenario,thelawpermitstheLicensingAuthoritytoabbreviate, deferoromitclinicaldatarequirements altogether.

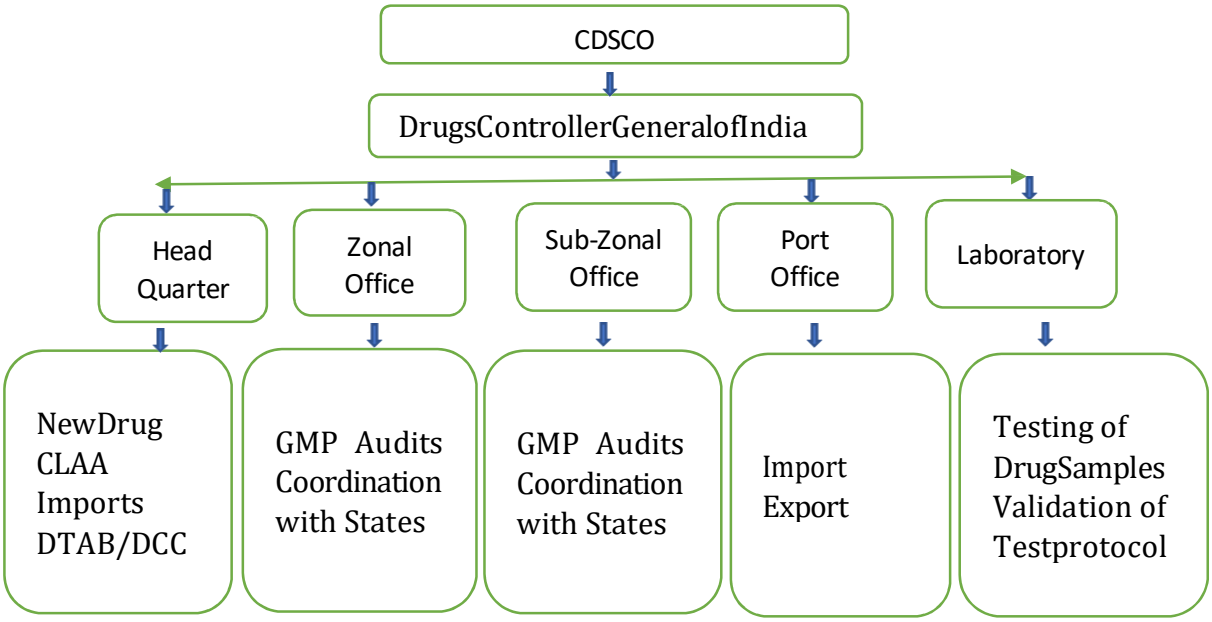
ApplicationsforapprovalofNewDrugsareevaluatedbythe12SubjectExpertCommittee (SEC) (formerly referredto as New Drug Advisory Committees (NDAC), consisting of experts usuallydrawnfromGovernmentMedicalCollegesandInstitutesacrossIndia.Theapprovalor otherwiseisgrantedbasedontherecommendationsofthesecommittees.Overall,thishasput considerablecloudoverthenewdrugsapprovalandregulatoryprocessinIndia,andwiththe banbeingissuedbythegovernmentratherthanbyCDSCO,thisparticularlycastsashadow on the legitimacy of CDSCO as a regulatory body.

Besides approval, the other important regulatory roles are regarding licensing and inspections. Sections22and23oftheDCActgivetheDrugInspectors(DI)thepowertoinspectpremises manufacturingorsellingdrugsorcosmeticsandtakesamplesofanydrugorcosmeticin exchangeofitsfairpriceandawrittenacknowledgement.Wherethesamplehasbeentaken fortestingoranalysis,theDImustinformaboutitspurposeinwritingtotheownerofthe premises.Theprovisionsalsodirectthe DItodividethesamplesintofour(three,iftakenfrom the manufacturer) properly sealed portions or take as many units of the drug. The Government Analyst under Section 25 of the DC Actmust then preparea signed report which is then taken to be a conclusive fact upon the standard of quality of the drug. These provisions are complemented bytheDC Rules which elaborateon the duties of the Government Analyst,the DrugInspectorandtheLicensingAuthority.

In 2017, the DC Rules were amended, making it mandatory that before the grant of manufacturinglicense,themanufacturingestablishmentistobeinspectedjointlybythe Drug Inspectors of both the central government and the concerned state government. The amendment alsomadeasimilarjointinspectionmandatoryformanufacturingpremisesfornotlessthat onceeverythreeyearsorasneededpertherisk-basedapproach.Recently,theDTABhas recommendedamendingtheDCActtoauthorizeLicensingAuthoritiestoissuestop-sale ordersfordrugretailers.Earlier,thispowertoissuestop-saleorderswasavailabletothe LicensingAuthoritiesincasesofmanufacturingnon-compliancesonly.

Organization ofCDSCO





Zonal offices

- Mumbai
- Kolkata
- Chennai
- Ghaziabad
- Ahemdabad
- Hyderabad

The zonaloffices work in close collaboration with theState DugControlAdministration and assist them in securing uniform enforcement of the drug act and other connected leistations, onallIndiabasis.TheseareinvolvedinGMPauditsandinspectionofmanufacturingunitsof largevolumeparental,sera,vaccineandbloodproducts.

Sub-zonaloffice:

I. Chandigarh
II. Jammu
III. Bangalore

These centre co-ordinate with state drug control authorities under their jurisdiction for uniform standardofinspectionandenforcement.

Functionsof PortOfficesofCDSCO

• Scrutiny of bills of entry with a view to ensuring that imported drugs comply with the regulations. •To check the shipping bills for export for statistical data andkeep control under the regulations

• To ensure that no New Drug is imported into the country unless its import is permitted by the Drugs Licensing Authority under Rules 122 A & 30-AA.

• To ensure that small quantities of drugs imported for clinical trials or for personal use are duly permittedunderTestLicense(11or11-A)orPermitLicenseas(12B)asthecasemaybe.
• MaintenanceofStatisticsregardingimportandexportofdrugsandcosmetics.

• Coordination withCustomsauthorities.

• CoordinationwithStatesDrugsControllersandZonalOfficesforpost-importchecks.
• Preparationofmonthly/quarterly/annualreports.

• Todrawsamplesfromimport/exportandre-importconsignments.

CentralDrugsTestingLaboratories(CDTL)

• CentralDrugLaboratory,Kolkata

• CentralDrugTestingLaboratory,Mumbai

• CentralDrugTestingLaboratory,Chennai

• CentralDrugLaboratory,Kasauli

• RegionalDrugTestingLaboratory,Guwahati

• RegionalDrugTestingLaboratory,Chandigarh

TheselaboratoriesareestablishedundertheIndianDrugandCosmeticAct,1940and responsiblefor qualitycontrol of drugs and cosmetics in the country.

Thefunctionsofthislaboratoriesinclude:

1. Statutoryfunctions:

a) AnalyticalqualitycontrolofmajorityoftheimporteddrugavailableinIndianmarket.
b) ActingasanAppellateauthorityinmattersofdisputesrelatingtoqualityofDrugs.
c) Layingdownstandards of drugs, cosmetics,diagnostics and devices.
d) LayingdownregulatorymeasuresamendmentstoActsandRules.
e) Toregulatemarketauthorisationofnewdrugs.

f) ToregulateclinicalresearchinIndia.

g) To approve licenses to manufacture certain categories of drugs as CentralLicence approving Authority i.e. for Blood Banks, Large Volume Parenteral and Vaccines & Sera.

h) Toregulatethestandardsofimporteddrugs.

i) WorkrelatingtotheDrugsTechnicalAdvisoryBoard(DTAB)andDrugs Consultative Committee (DCC).

j) TestingofdrugsbyCentralDrugs Labs

k) PublicationofIndianPharmacopoeia.

2. Otherfunctions:

i) Collection, storage and distribution of International Standard reference preparations ofDrug&Pharmaceuticalsubstances.

ii) Training ofDrug Analysts deputed byStateDrug ControlLaboratories and other Institutions.

iii) ToadvisetheCentralDrugControlAdministrationinrespectofquality& toxicity of drug awaiting licence.

iv) ToworkoutanalyticalspecificationsforpreparationofMonographsfortheIndian Pharmacopeia&theHomeopathicPharmacopeiaofIndia.

v) MonitoringintheWHOGMPcertificationscheme.

vi) Screening ofdrug formulationsavailableinIndianmarket.

vii) Evaluation/screeningofapplicationsforgrantingNOCforexportofunapproved /banneddrugs.

Functions ofCDSCOinCentre

- Approvalofnewdrugsandclinicaltrials.
- ImportRegistrationandLicensing
- Licensing of Blood Banks, LVPs, Vaccines, r-DNA products and someMedical devices and Diagnostic agents.
- AmendmenttoD&CActandRules.
- ParticipationinWHOGMPcertificationschemes.
- Banningofdrugsandcosmetics.
- Granttotestlicense,personallicense,NOC'sforexport.
- TestingofdrugsbyCentralLabs.
- PublicationofIndianPharmacopoeia.

- Monitoringadversedrugreactions.
- GuidanceonTechnical matters.

ResponsibilitiesofCentral Authority

CDSCO:Forimplementingandtorevisethesameasnotified,fromtimetotimebythe authority.

• Initiateinframingofrules,regulationsandguidancedocumentstomatchthecontemporary issues in compliancewith therequirements of Drugs &Cosmetics Act 1940 and Rules1945.

• Facilitate in Uniform implementation of the provisions of the Drugs & Cosmetics Act 1940 and Rules 1945.

• FunctionasCentrallicenseApprovingAuthorityundertheprovisionsofDrugsand Cosmetics Act 1940 and Rules 1945.

• CollaborationwithothersimilarInternationalagencies.•ProvidingtrainingtotheIndian regulatorypersonnel.

• ApprovalofNewDrugs

• ClinicalTrialsinthecountry

• LayingdownthestandardsforDrugs

• Controloverthequalityofimported Drugs

• CoordinationoftheactivitiesofStateDrugCO

• Providing expert advice witha view of bringing about the uniformityin the enforcement of the Drugs and Cosmetics Act

DrugTechnical AdvisoryBoard(DTAB)

Ex-Officio:

(i) DirectorGeneralofHealth Services(Chairman)
(ii) Drugs Controller, India
(iii) DirectoroftheCentralDrugsLaboratory,Calcutta
(iv) DirectoroftheCentral ResearchInstitute,Kasauli
(v) PresidentofMedicalCouncilofIndia
(vi) PresidentofthePharmacyCouncilofIndia

(vii) DirectorofCentralDrugResearchInstitute,Lucknow

Nominated:

1) TwopersonsbytheCentralGovernment.

2) OnepersonbytheCentralGovernmentfromthepharmaceuticalindustry

3) TwopersonsholdingtheappointmentofGovernmentAnalystunderthisAct,

Elected:

1) Oneperson,tobeelectedbytheExecutiveCommitteeofthePharmacyCouncilofIndia,

2) One person, to be electedbythe ExecutiveCommittee ofthe Medical Council ofIndia,

3) One pharmacologist to beelected bythe GoverningBodyofthe Indian Council of Medical Research;

4) OnepersontobeelectedbytheCentralCouncilofthelndianMedicalAssociation;

5) One personto beelectedbytheCouncilofthelndianPharmaceutical Association

Function:

ToadvisetheCentralGovernmentandtheStateGovernmentsontechnicalmatters.Tocarry outtheotherfunctionsassignedtoitbythisAct.

TheDrugsConsultativeCommittee(DCC)

- Itisalsoanadvisorybodyconstitutedbycentralgovernment.

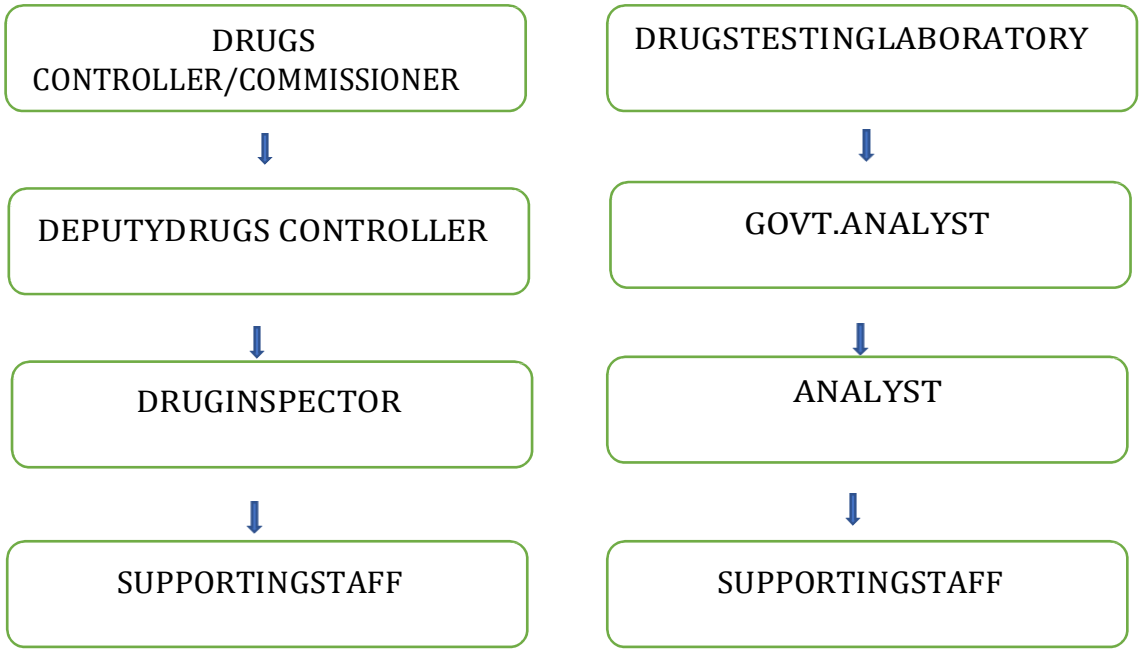
Constitution:

- TworepresentativesoftheCentralGovernment
- OnerepresentativeofeachStateGovernment

Functions:

- ToadvisetheCentralGovernment,theStateGovernmentsandtheDrugsTechnical AdvisoryBoardonanyothermattertendingtosecureuniformitythroughoutIndia intheadministrationofthisAct.
- There isseparate "The Ayurvedic, Siddha, & Unani Drugs Consultative Committee constitutedundersec33DoftheAct.

STATEDRUGS CONTROL ORGINATION



StateDrugRegulatoryAuthorities(SDRAs)establishedundertheDCActareresponsible forlicensingofmanufacturingestablishmentsandsalepremises,undertakinginspectionsof such premises toensurecompliancewithlicenseconditions, drawing samples for testing and monitoring of quality of drugs, taking actions like suspension/cancellation of licenses, surveillanceover sale of spurious and adulterated drugs, institutinglegal prosecution when required,andmonitoringofobjectionableadvertisementsfordrugs.

The State Drug Controller (SDC) heads the SDRA and reports toa joint secretaryin the health departmentofthestategovernment.AtypicalSDRAhasDrugInspectorsreportingtothe DeputyDrugsControllerwhoalsoactsastheLicensingAuthorityforthestate.Administrative matterssuchasdepartmentalbudgeting,appointments,trainingofofficers,andallotmentof fundsandresourcesforinspections,fallsunderthejurisdictionofthestategovernments.This report found that a numberof SDRAs wereconjoined with the food regulatorydepartments (FDAs)ofthestate,makingitdifficulttoclearlydemarcatetheavailablefundsandresources between the two.

Functionof StateLicensingAuthorities

1. Licensingofdrugmanufacturing andsalesestablishments
2. Licensingofdrugtestinglaboratories.
3. Approvalofdrugformulationsformanufacture.

4. MonitoringofqualityofDrugs&Cosmetics,manufacturedbyrespectivestateunits andthosemarketedinthestate.

5. Investigationandprosecutioninrespectofcontraventionoflegalprovisions.

6. Administrativeactions.

7. Pre-andpost-licensing inspection

8. Recall ofsub-standarddrugs.

ResponsibilitiesofStateAuthority

• Manufacturing,sales,distributionofDrugslicensingdrugtestinglaboratories.

• Approvingdrugformulationsformanufacture

• Carryingoutpre-andpost-licensinginspections

• Overseeing the manufacturing processfordrugsmanufacturedby respectivestateunitsandthosemarketedinthestate

CertificateofPharmaceuticalProduct(COPP)

Definition-

The WHO Certification Scheme for a Certificate of Pharmaceutical Product (COPP) is an internationalvoluntaryagreementtoprovideassurancetocountriesparticipatinginthe Scheme,aboutthequalityofpharmaceuticalproductsmovingininternationalcommerce.

CertificateofpharmaceuticalproductisaschemedevelopedbytheWHOinresponsetothe requestofWHOMemberStatestofacilitateinternationaltradeinpharmaceuticalproducts betweenMemberStates.Itwasfirstdevelopedin1975.Sincethenithasbeenrevisedin1988, 1992and in 1997.

Purpose-

ACOPPisintheformatrecommendedbytheWHO.Itistheimportingcountrywhorequires the COPP for the pharmaceutical product and a special type of certificate which enables a given pharmaceutical product to be registered and marketed in the exporting country of interest and formspartsofthemarketingauthorizationapplication.

This certificate describes the characteristics of the medicinal product approved in the exporting country,includesinformationabouttheapplicantofthecertificateandisaccordingwiththe modelrecommendedbytheWorldHealthOrganization.Thisisacertificateissuedbythe Inspectorate establishing the status of the pharmaceutical, biological,radiopharmaceutical or veterinaryproductlisted andtheGMPstatusofthefabricatoroftheproduct.

Ideally,aCOPPshouldnotberequiredincountriesthathavethecapabilitiestoconductfull reviews. The COPPshould be usedwhen apharmaceutical product isunderconsideration for a product licence/marketing authorisation or when administrative action is required to renew, extend or varysuch a licence.

AimandScope-

TheCOPPisthelegaldocumentthatdeclaresacertainmanufacturingcompanyislegally allowed to sell their pharmaceutical product in the country they are producing.When registering a pharmaceutical product overseas, the Government body in charge of approving the application will usually require a COPP to ensure that the product is being sold as a commercial finishedproduct in the countrythat is producingit.

ACOPPdemonstratesinquestionthattheimportedmedicineisoftheappropriatestandardof quality,safetyandefficacytoallowmarketingintheirmarket,havingundergonerigorous testing and examination to Regulatory Authorities in the exporting country and also demonstratesthatitfollowsthecorrectguidelinesandproceduresofGoodManufacturing Practice(GMP),increasingthelevelofqualityandindeedsafetyoftheproduct.TheCOPPis neededwhentheproducttendsthatitisintendedforregistrationoritsrenewal(licensing, authorizationorprolongation))bytheimportingcountry,withthescopethattheproductis distributed orcommercializedin that country.

Certification has been recommended by WHO tohelp undersized drug regulatory authorities or drug regulatory authorities without proper quality assurance facilities in importing countriestoassessthequalityofpharmaceuticalproductsasprerequisiteofregistrationorimportation.

Need &Importanceof COPP:

Toobtain globalmarketingapproval for anypharmaceuticalproduct(whetherintendedfor animal/human use) one of the key documents required is a COPP, which has been recommendedbytheWHO.ACOPPisissued bythe authorizedbodyof theexportingcountry andisintendedforuse bythe competentauthoritywithinanimportingcountry: when a pharmaceuticalproductisunderconsiderationforaproductlicense/marketingauthorization that will authorize its importation and sale in the importing country; when administrative action isrequiredtorenew,extendvaryorreviewsuchlicense.

ACOPPisissuedforhumandrugs(pharmaceutical,biologicalandradiopharmaceutical)as well as for veterinary drugs (food producing animals and non-food producing animals). For eachmedicinalproduct(TradeName/PharmaceuticalForm/Strength)isissuedacertificate statingthecountrytoexport.TheseCertificatesareissuedtothemarketingauthorizations holders (MAH) for medicinal products (with valid Marketing Authorization) or their representatives, manufacturers (without Marketing Authorization and with manufacturing authorization valid) or wholesale distributor authorized by the MAH to consult the information forthemedicinalproduct(s)

Types ofCOPP:

1) WHO 1975 type COPP-

The WHO 1975 versionis a certificate to be issued by exporting country regulatory authority stating:a)theauthorizedproducthastobeplacedonthemarketforitsuseinthecountryalso,

the permit number and issuedate, orb) that the nonauthorized producthas placed on themarket for its use in the country and also add the reasons why it is needed; Also, that; a) As recommended by World Health Organization, the manufacturer of product conforms to GMP requirements.b) onlywithin the countryoforigintheproductsto be sold or distributed; or c) To be exported to manufacturing plant where the product is produced and at suitable intervals subject to inspections.

2) WHO 1988 type COPP-

UnliketheWHO1975version,thecompetentauthorityoftheexportingcountryshouldhave: alllabellingcopiesandproductdetailedinformationinthecountryoforigin.

3) **WHO1992 typeCOPP-**

Thisisintendedfor use bythecompetentauthorityofanimporting countryintwo situations:
a) When the question arises related to importationand salelicense; and b) For license renew, extend, reviewor changes.

Thefollowinginformationrequiredforthecertificate:

i) Whetheralicensedproductisrequiredtobeplacedonthemarketornot.
ii) Alsoifthesatisfiedinformationsubmittedbytheapplicantthatthecertifying authorityof the manufactureoftheproduct undertaken byanotherparty
iii) iii)Inspectionhavebeencarriedoutofthemanufacturerofproduct;
iv) Ifthecertificateisprovisionalorpermanent;
v) Is the dosage forms, packages and/or labels of a finished dosage form manufactured byanindependentcompanyorbytheapplicant;
vi) statesthenamesoftheimportingandexporting(certifying)countries

HerebesidesthreetypesofCOPPs alsowehaveanotherspecifictypeoftheU.S.FDACOPPs. The U.S.FDA issued "Pilot- COPP" for the remaining products which areneither exported nor manufactured in the United States.It is onlywhenno other countryhasgiven an approval for thefinishedmedicinalproductregistration.

Contentof the COPP

ACPPhastwodistinctparts:a)Evidenceofquality,safety,andefficacy(QSE)Reviewand
b) EvidenceofCompliancewithGMP.

Contentandformat

- Importingcountry:
- Exportingcountry:
- Name,formofdosageanditscompositionoftheproduct(APIperunitdose).
- RegistrationInformation(licensing)
- Marketingstatusoftheproductintheexportingcountry.
- licenseno. of product (containinglicenseholderdetails; involvement of licenseholder inmanufacturingifany)andalsoadddateofissue,
- Summaryoftechnicalbasisonwhichtheproducthasbeenlicensed(ifrequiredbythe issuing authority)
- Currentlymarketedproduct'sinformation
- Detailsabouttheproduct'sapplicant
- Iflackingisthereintheexportingcountry,needtomentiontheinformationabout reasons.

Key challengesof theinterpretationoftheCOPPscheme

- Differenceinproductnamesbetweencertifyingandrequestingcountries.
- TheCOPPconfirmsGMPstatus,additionalGMPcertificatesshouldnotbenecessary.
- TheCOPPisalegaldocument,additionalapostilleand/orlegalizationshouldnotbe requested.
- Requirementsforthe'countryoforigin'or'sourcecountry'havemultipledefinitions and should beclarifiedasit could refertothe countryof anyone ofthe following: first approvalormarketing,manufacture,packaging,finalrelease,ormainheadquartersof thepharmaceuticalcompany.
- TheCOPPprovidesevidenceofapositiveQSEreviewintheissuingcountry.Afull dossiershouldnotberequested.
- Theschemerefersonlytothemanufacturerofthedosageformbutsomeimporting countriesrequireadditionalmanufacturerstobelisted.
- TheCOPPissuedisasnapshotoftheMarketAuthorization(MA)intheissuingcountry andmaynotnecessarilyreflecttheentiresituationintheimportingcountry.

Advantagesofthescheme

- Togrowbusinessinforeigncountry,necessarytoobtaintheCOPPcertificatesby pharmaceuticalcompanies.
- TheSchemeprovidesthestandardformatthatisexpectedtobeused.

- Enables recipient COPP countries to gain assurance on the QSE of the product in the issuing country.
- Obligescertifyingauthoritiestodiscloseimportantinformationtotheimporting country.
- By supporting the review and approval process it facilitates patient access to quality medicines.

The COPP maybe requiredtosupport a regulatorysubmission. This can besubmitted at the beginning of, or during the health authority review. According to the WHO Scheme, COPPsshould not be required in countries that require fullICH CTD dossiers andhavethecapabilitytoconductfullQSEreviews.

TheCOPPonlyreflectstheapprovedmanufacturingsourcingrouteofthecertifying country.

Mostrecipientauthoritiesexpectthatthedrugproducttheywillreceivemirrorsthat whichhasbeenapprovedbytheauthorityissuingtheCOPP.Whendevelopingaglobal submissionstrategyCOPPrequirementsareconsideredearlyduringtheplanning phase. If required HAs should be open to discussion in advance of the regulatory submissiontogiveadviceandagreeonthecontentofthesubmissionincludingthe COPP to move forward as quicklypossible.

Certificateof apharmaceuticalproduct

This certificate, which is in the format recommended byWHO, establishes the status ofthepharmaceuticalproductandoftheapplicantforthecertificateintheexporting country. It is for a single product only since manufacturing arrangements and approved informationfordifferentdosageformsanddifferentstrengthscanvary.

TheCOPPprovidestheinformationofthefollowing:

1. **CertificatenumberofCOPP**:ThecertificatenumberofCOPPshouldbeenclosed inthespecifiedformatrecommendedbyWHO.
2. **Name of exporting country i.e. (certifying country):** The name of the country (certifiedcountry)towhichtheproductisbeingexportedmustbementionedinthe certificate.
3. **Nameofimportingcountryi.e.(requestingcountry):**Thenameofthecountries (requesting countries) from which the product is being imported from certified country mustbementionedinthecertificate.
4. **Nameanddosage formoftheproduct:**

TableNo.1: Essentials ofProduct

Active ingredient	InternationalNon-proprietaryNames(INNs)or nationalnon-proprietarynames
Amountperunitdose	Theformula(completecomposition)ofthedosage formshouldbegivenonthecertificateorbe appended.
Completecompositionincluding excipients	Detailsofquantitativecompositionarepreferred but their provision is subject to the agreement of the product-licenseholder.
Isthisproductlicensedtobe placedonthemarketforusein the exportingcountry?(yes/no)	Whenapplicable,appenddetailsofanyrestriction applied to the sale, distribution or administration of the product that is specified in the product license.

5. **Statusof the productactuallyonthe marketin theexportingcountry**:

Iftheproductisactuallymarketedin theexportingcountry,theCOPPshouldbe provided with the following details:

- Number of product license and date of issue: Indicate, when applicable, if the licenseis provisional,or theproducthasnot yetbeenapproved.
- Productlicenseholder(nameandaddress):
- Statusof product licenseholder:
  Specifywhetherthepersonresponsibleforplacingtheproductonthemarket:

a) manufacturesthedosageform;
b) packagesand/orlabelsadosageformmanufacturedbyanindependent company; or
c) isinvolvedin noneoftheabove.

- **Forcategoriesbandc**thenameandaddressofthemanufacturerproducing thedosage formis This informationcanonlybe providedwith the consentof the product-license holder or, in the case of non-registered products, the applicant. Non-completion of this section indicates that the party concerned has not agreedto inclusion of thisinformation. It should benoted thatinformation concerning the site of production is part of the product license. If the production siteischanged,thelicensehastobeupdatedoritisnolongervalid.
- Isasummarybasisforapprovalappended?(yes/no)

Thisreferstothedocument,preparedbysomenationalregulatoryauthorities, thatsummarizesthetechnicalbasisonwhichtheproducthasbeenlicensed.

- Is the attached, officially approved product information complete and consonent with the license? (yes/no/not provided)
  This refers to product information approved by the competent national regulatory authority, such as Summary Product Characteristics (SPC).
- Applicantforcertificate,ifdifferentfromlicenseholder(nameandaddress)
  In thiscircumstance, permission for issuingthecertificateisrequiredfrom the product-license holder. Thispermission has to be provided to the authority by the applicant.

6. **Periodicinspectionofthemanufacturingplantbythecertifyingauthority:**

Ifthecertifyingauthorityarrangeforperiodicinspectionofthemanufacturingplantin whichthedosageformisproduced,thefollowingdetailsweretobeincludedinthe COPP.

- Periodicityofroutineinspections(years):
- Hasthemanufactureofthistypeofdosageformbeeninspected?(yes/no)
- DothefacilitiesandoperationsconformtoGMPasrecommendedby theWorld HealthOrganization?(yes/no/notapplicable)

7. **The information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product undertaken by another party:**

Thissectionistobecompletedwhentheproduct-licenseholderorapplicantconformstostatus (b) or (c) as described in note above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stageofmanufactureofthefinisheddosageform,andtheextentandnatureofanycontrols exercisedovereachoftheseparties.

8. **Otherdetailsof Manufacturingpremises:**

ThefollowingdetailswhichistobeenclosedintheCOPPare,

- Address ofcertifyingauthority
- TelephoneandFax
- Nameofauthorizedperson
- Signature

- Stampanddate

Howto obtainCOPP?

- To obtain a COPP, a request ismade to the exportingcountry's healthauthoritybythe Marketing Authorization Holder (MAH).
- AnauthorizedpersonissuestheCOPPandreturnsittotheMAH.Alsootherdocuments required to obtain a COPP including an application for Export Certificate form, evidence of a GMP certificate (if applicable), Manufacturing License and the last approvedSPC (SummaryofProductCharacteristics).

Typesof drugsforwhichCOPPs maybeissued

- Approveddrugproducts
- Activepharmaceuticalingredients(API)
- Overthecounterdrug(OTC)products
- Unapproveddrugproducts
- Homeopathicdrugs

WhocanapplyforCOPP?

- A complete application for export certification must be submitted by the person/companywhoexportsthedrug.
- The certification isintended for a drug which : meets the applicable requirements of the Act or Food Drug and Cosmetic Act 801(e)(1) requirements [21 U.S.C.381(e)(1)]

Processto applyfora COPP

a) Submit Form no. 3613b– Located on the FDA internet www.fda.gov/downloads/AboutFDA/Reports Manuals Forms/Forms/UCM052388

b) RequirementsforCOPPapplication:

- Applicant ContactInformation
- Tradename(thedrugproduct'sbrandname)
- BulkSubstanceGenericName
- NameofApplicant
- StatusofProductLicenseholder
- ListingofmanufacturinglocationonCOPP
- CompleteManufacturingFacilityAddress
- FacilityRegistrationNumber
- Importingcountries

- AuthorizationtoRelease Information
- Number ofcertificatesrequested
- CertificationStatement
- Billingcontact
- Marketing StatusintheExporting Country

ProcessTimeof COPP:

- Drugsincomplianceare normallyissued withintwenty(20)governmentworking daysofreceiptofcompleteandanaccurateCOPPapplication.

Certificatesmaynotbeissued

- Returned–missinginformationapplicationwithaletteridentifyingthemissing information.
- Rejected–manufacturingfacilitiesarenotincompliancewithgoodmanufacturing practices (GMPs).
- Denied–drugproductsarenotcomplianceasperregulation(e.g.,misbranded drug)

ExpirationofCOPP

- Certificateexpireson2yearsfromthenotarizationdateorasnoted.Afterexpiry date,anewCOPPapplicationhastobesubmitted.

FormatofCertificateofPharmaceuticalProducts(COPP)(asperWHOGMP guidelines)

No.ofCertificate: ----------

Exporting(certifying)country: ----------

Importing (requesting) country: ----------

Nameanddosageformofproduct: ----------

Activeingredient(s)andamount(s)perunitdose:----------

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1. IsthisproductLicensedtobeplacedonthemarketforuseintheexportingcountry?IfYes, complete Box A. If No complete Box B.

A.

Product-licenseHolder(nameandaddress):-

StatusoflicenseHolder-a/b/c(keyinappropriatecategory)

NumberofproductLicenseanddateofissue:----------

Isanapprovedtechnicalsummaryappended?Yes/No

Istheattached,officiallyapprovedproductinformationcompleteandconsonantwiththe License?Yes/no/notprovided(keyinasappropriate)

Applicantforcertificate,ifdifferentfromLicenseholder(nameandaddress):----------

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B.

Applicant for certificate (name and address): ----------

Status of applicant:a/b/c (key in appropriate category)

Whyismarketingauthorizationlacking?

Notrequired/notrequested/underconsideration/refused(keyisasappropriate) Remark:

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2. Does the certifying authority arrangefor periodicinspectionofthemanufacturing plantin which the dosage form is produced?Yes/no/notapplicable (keyin asappropriate)

Ifnoornotapplicableproceedtoquestion3.

Periodicityof routineinspections (years):----------

Hasthemanufactureofthistypeofdosageformbeeninspected?Yes/no(keyinas appropriate)

Do the facilities and operationsconform to GMP as recommended by the World Health Organization?15Yes/no(keyinasappropriate)

3. Does the information submitted by the applicant satisfy the certifying authority on all aspectsofthemanufactureoftheproduct?Yes/no(keyinasappropriate)

Ifno,explain: ----------

Address ofcertifyingauthority: ----------

Telephone number:---------- Faxnumber: ---------- ----------

Nameofauthorizedperson: ----------

Signature:----------

Stampanddate: ----------

ApprovalofNew DruginIndia

If any company in India wants to manufacture or import a new drug, they need to apply to seekpermissionfromthe licensingauthority(DCGI)byfilingin Form44 alsosubmittingthedata

asgiveninScheduleYofDrugsandCosmeticsAct1940andRules1945.Toproveitsefficacy andsafetyinIndianpopulationtheyneedtoconductclinicaltrialsinaccordancewiththe guidelinesspecifiedinScheduleYandsubmitthereportofsuchclinicaltrialsinspecified format.

Demonstrationofsafetyandefficacyofthe drug product forusein humans is essentialbefore the drug product can be approved for import or manufacturing of new drug by the applicant by CentralDrugsStandardControlOrganization(CDSCO).TheregulationsunderDrugsand Cosmetics Act 1940 and its rules 1945, 122A, 122B and 122D describe the information requiredforapprovalofanapplicationtoimportormanufactureofnewdrugformarketing. For an investigational new drug, the sponsor needs to provide detailed information to the DCGI about:

1. Genericname
2. Patentstatus
3. Briefdescriptionofphysico-chemical/biological
4. Technicalinformation like

   a)Stability b)Specifications c)Manufacturing process d)Worldwideregulatory status e) Animalpharmacologyandtoxicitystudies
5. Publishedclinicaltrialreports
6. Proposedprotocolandproforma
7. Trialduration
8. Duringmasterfile
9. UndertakingtoReportSerious orLife-threateningAdverseDrugReactions.

The information regarding the prescription, samples and testing protocols, product monographs,labelsmust alsobesubmitted.Itusually takes 3monthsfor clinicaltrialapprovalinIndia.TheclinicaltrialscanberegisteredintheClinicalTrialsRegistryofI ndia(CTRI) giving details of the clinical trials and the subjects involved in the trials. The rules to be followedunderTheDrugsandCosmeticsRules1945are:

1. Rule122A-:Applicationforpermissiontoimportnewdrug
2. Rule 122 B- Application for approval to manufacture new drug other than the drugs specified under Schedule C and C (1).
3. Rule 22 D- P Application for permission to import or manufacture fixed dose combination.

4. Rule122DA-ApplicationforpermissiontoconductclinicaltrialsforNew Drug/InvestigationalNewDrug
5. Rule122E-DefinitionofNewDrugs*

There'saprovisioninRule-122AofDrugandCosmeticAct1940andRules1945,thatifthe licensingauthorityfindsoutthatifeverythingisintheinterestofpublichealththenhemay allowtheimportofnewdrugs,basedonthedataofthetrialsdoneinothercountries.Another provisionisRule-122Aisthatclinicaltrialmaybeallowedinanynewdrugcase,whichare approvedandalreadybeingusedformanyyearsinothercountries.

Similarly,inRule122-B,applicationforapprovaltomanufactureNewDrugotherthanthe drugsclassifiableunderSchedulesCandC(1)andPermissiontoimportormanufacturefixed dose combination (122-D).

Purpose-

The main purpose of regulating all the medicinal products by regulatory agencies is to safeguardpublichealth.Regulatoryagenciesworkistomakesurethatthepharmaceutical companiescomplywithal,theregulationsandstandards,sothatthepatient'swell-beingis protected.

Through the International Conference on Harmonization (ICH) process, the Common TechnicalDocument(CTD)guidancehasbeendevelopedforJapan,EuropeanUnion,and United States.

MostcountrieshaveadoptedtheCTDformat.Hence,CDSCOhasalsodecidedtoadoptCTD format for technicalrequirements for registration of pharmaceuticalproducts for humanuse.

It is apparent that this structured application with comprehensive and rational contents will help the CDSCO to review and take necessaryactions in a better wayand would also ease the preparationofelectronicsubmissions,whichmayhappeninthenearfutureatCDSCO.

NewDrug Application(NDA)

New Drug Application (NDA) is an application submitted to the individual regulatory authorityforauthorizationtomarketanewdrugi.e.innovativeproduct.Togainthispermission a sponsor submits preclinical and clinical test data for analyzing the drug information, description of manufacturing procedures.

AfterNDAreceivedbytheagency,itundergoes a technicalscreening.Thisevaluationensures thatsufficientdataandinformationhavebeensubmittedineachareatojustify“filing”the application thatis FDAformal review.

At the conclusion of FDA review of an NDA, there are 3 possible actions that can send to sponsor:

- Notapprovable-inthisletterlistofdeficienciesandexplainthereason.
- Approvable-itmeansthatthedrugcanbeapprovedbutminordeficienciesthatcanbe correctedlike-labellingchangesandpossiblerequestcommitmenttodopost-approval studies.
- Approval-itstatethatthedrugisapproved.

Iftheactiontakeniseitheranapprovableoranotapprovable,thenFDAprovidesapplicant with an opportunityto meet with agencyand discuss the deficiencies.

DifferentPhasesofclinical trials:

- Pre-clinicalstudy-Mice,Rat,Rabbit,Monkeys
- PhaseI- Humanpharmacologytrial-estimationof safetyandtolerability
- PhaseII-Exploratorytrial-estimationof effectiveness andshort-termsideeffects
- PhaseIII-Confirmatorytrial-Confirmationoftherapeuticbenefits
- PhaseIV -Postmarketingtrial-Studiesdoneafterdrugapproval

Some of the rules & guidelines that should be followed for regulation of drugs in India are:

- DrugsandCosmeticsAct1940anditsrules1945
- Narcotic Drugs andPsychotropic Substances-1985
- DrugsPriceControlOrder1995
- Consumer ProtectionAct-1986
- FactoriesAct-1948
- LawofContracts(IndiancontractAct-1872)
- Monopolistic&RestrictiveTradePracticesAct-1969
- ICHGCPGuidelines
- ScheduleY Guidelines
- ICMRGuidelines

- RegistryofTrial

Stages ofapproval-

1. SubmissionofClinicalTrialapplicationforevaluatingsafetyandefficacy.
2. Requirementsforpermissionofnewdrugsapproval.
3. Postapprovalchangesinbiologicalproducts:quality,safetyandefficacydocuments.
4. Preparationofthequalityinformationfordrugsubmissionfornewdrugapproval.

1. Submission of ClinicalTrialApplicationforEvaluatingSafetyandEfficacy:

Allthedatalistedbelowhastobeproduced.

(a) Phase-I&phase-IIclinicaltrial:

I. Generalinformation
- Introductionaboutcompany:Briefdescriptionaboutcompany
- Administrativeheadquarters:Provideaddressofcompanyheadquarters
- ManufacturingFacilities:Provideaddressofcompanyheadquarters
- Regulatoryandintellectualpropertystatusinothercountries.
- PatentinformationstatusinIndia&othercountries

II. Chemistrymanufacturingcontrol
- ProductDescription:Abriefdescriptionofthedrugandthetherapeuticclassto whichit belongs.
- ProductDevelopment
- Straindetails
- Informationondrugsubstance
- InformationondrugProduct

III. Non-clinicaldata:References:schedule–Y,amendmentversion2005,Drugsand Cosmetics Rules, 1945

IV. Proposedphase-I/IIstudies:protocolforphase-I/IIstudies

(b) Phase-IIIclinicaltrial:

Allthe information is as same as phase-I&phase-IIclinicaltrial
- Generalinformation
- Chemistrymanufacturingcontrol

- Non-clinicaldata
- Proposedphase-IIIstudies

2. RequirementsforpermissionofNewDrugsApproval

The manufacturer / sponsor have to submit application on Form 44 for permission of New Drugs Approval under the provisions of Drugs and Cosmetic Act 1940 and Rules 1945. The document design is as per the International submission requirements of Common Technical Document (CTD) and has five Modules.

ModuleI:Administrative/LegalInformation

Thismoduleshouldcontaindocumentsspecifictoeachregion;forexample,applicationforms orthepropos edlabelforuseintheregion.Thecontentandformatofthismodulecanbe specified bythe relevant regulatoryauthorities.

ModuleII: Summaries

Module 2 should begin with a general introduction to the pharmaceutical, including its pharmacologicclass,modeofactionandproposedclinicaluse.Ingeneral,theintroduction should not exceed one page. The introduction should include proprietary name, nonproprietary nameorcommonnameofthedrugsubstance,companyname,dosageform(s),strength(s), route of administration, and proposed indication(s). It contains the CTD summaries for quality, safety, efficacyinformation. This moduleis veryimportant,as it provides detailed summaries ofthevarioussectionsoftheCTD.Theseinclude:Averyshortintroduction.Qualityoverall summary, Non clinical overview, Clinical over view, Non clinical written and tabulated summariesforpharmacology,pharmacokinetics,andtoxicology.

ModuleIII:Qualityinformation(Chemical,pharmaceuticalandbiological)

Informationonqualityshouldbepresentedinthestructuredformatdescribedintheguidance M4Q. This document is intended to provide guidance on the format of a registration application fordrugsubstancesandtheircorrespondingdrugproducts.Itcontainsofallofthequality documents for the chemistry, manufacture, and controls of thedrugsubstanceand the drug product.

ModuleIV:Non-clinical information

Informationonsafetyshouldbepresented inthe structuredformatdescribed inthe guidance M4S.Thepurposeofthissectionistopresentacriticalanalysisofthenon-clinicaldata

pertinent to the safety of the medicinal product in the intended population. The analysis should consider all relevantdata, whether positive or negative, and should explain why and how the datasupportthepproposedindicationandprescribinginformation.Itgivesfinalcopyofallof thefinalnonclinicalstudyreports.

Module V:Clinicalinformation

Information on efficacy should be presented in the structured format described in the guidance M4E. It gives clinical summary including biopharmaceutics, pharmacokinetics and pharmacodynamics, clinical pharmacologystudies, clinical efficacy, clinical safety, synopses oftheindividualstudiesandfinalcopyofdetailedclinicalstudyreports.

3. Preparationof the qualityinformation fordrug submissionfornewdrug approval

1) Drugsubstance(name,manufacturer)

2) Characterization(name,manufacturer)

- Physicochemicalcharacterization
- Biologicalcharacterization

3) Drugproduct(name,dosageform)

4) Controlofdrugproduct(name,dosageform)

5) Appendices

- Facilitiesandequipment(name,manufacturer)
- Safetyevaluationadventitiousagents(name,dosageform,manufacturer).

FeesforClinicalTrial/Approval of NewDrugs

• PhaseI(IND)-Rs.50000

• PhaseII(IND)-Rs.25000

• PhaseIII(IND)-Rs.25000

• ApprovalofNewMolecule-Rs.50000

• ApprovedNewDrug: Within1Yrofapproval-Rs.50000

After 1yr of approval -Rs.15000

• ApprovalofNewclaim,NewDosageformetc.Rs.15000

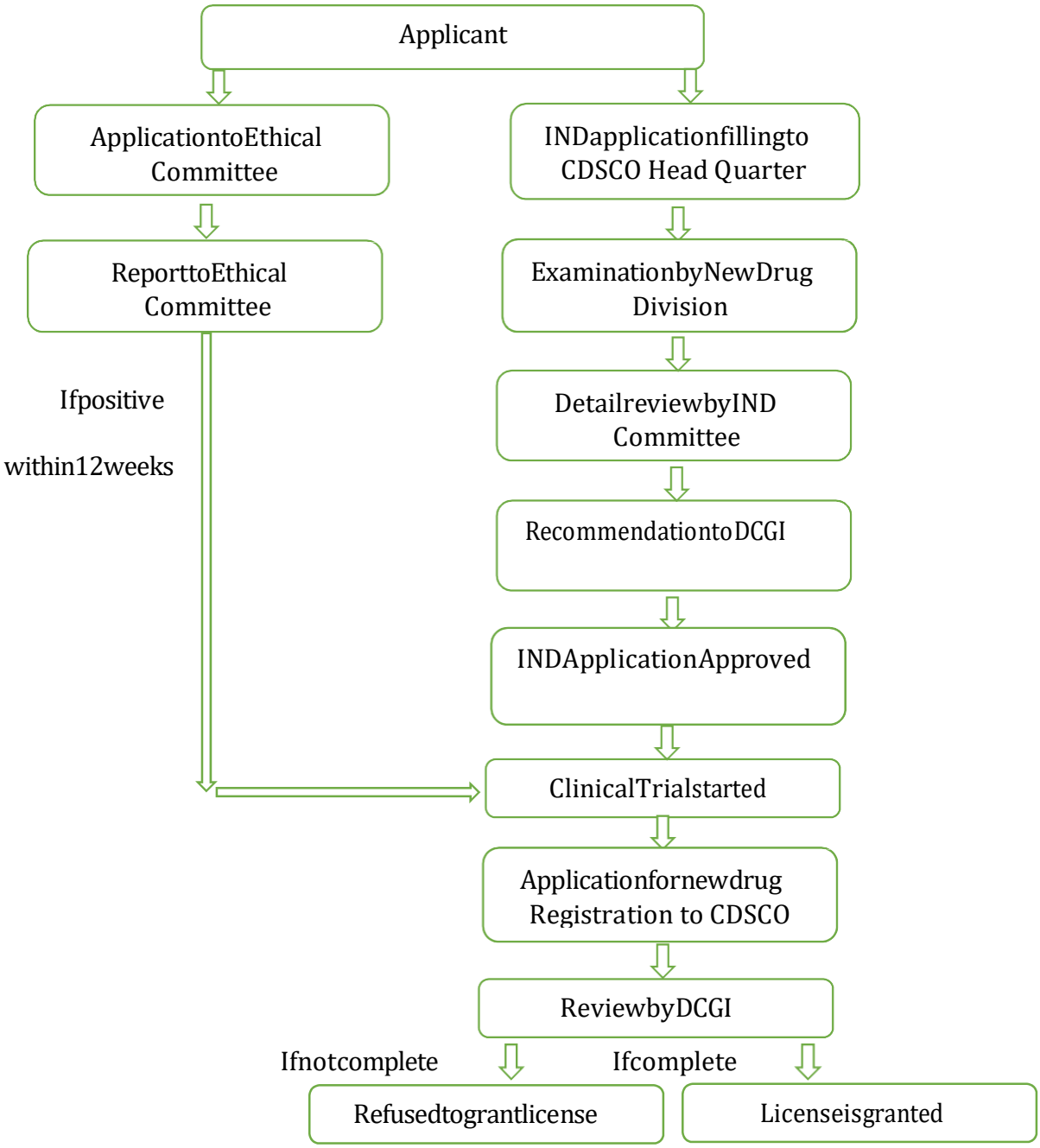

Fig.1.DrugApprovalprocessinIndia

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