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A STUDY OF CMC , POST APPROVAL REGULATORY AFFAIRS

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Abstract

Chemistry, Manufacturing and Controls (CMC) is a critical component of regulatory submissions that ensures the quality, safety, and efficacy of pharmaceutical products. Post-approval CMC activities focus on managing changes after a drug product has received marketing authorization. These changes may occur in raw materials, manufacturing processes, equipment, facilities, or analytical methods. Regulatory authorities require that all post-approval changes are properly evaluated, documented, and reported .The main objective of post-approval CMC is to maintain consistent product quality throughout the product lifecycle .Any modification should not adversely affect the identity, strength, quality, purity, or potency of the drug product.Post-approval changes are classified based on their potential impact on product quality.Common categories include minor, moderate, and major changes.Different regulatory pathways are followed depending on the risk level of the change.Regulatory agencies such as US FDA, EMA, and CDSCO provide guidelines for post-approval CMC changes.In the US, changes are reported through supplements like PAS, CBE-30, or annual reports.Stability studies play an important role in supporting post-approval changes.Validation and re-validation of processes are often required after significant changes.Change control systems ensure proper evaluation and approval of modifications.Post-approval CMC documentation includes updated specifications, batch records, and validation reports.Continuous monitoring of manufacturing processes is essential for compliance.Quality Risk Management (QRM) tools are applied to assess the impact of changes.Post-approval CMC activities support product lifecycle management.They also help in scale-up, site transfer, and technology transfer.Regulatory compliance during post-approval ensures uninterrupted product supply.Failure to report changes may lead to regulatory action.Post-approval inspections verify compliance with approved CMC information.Good Manufacturing Practices (GMP) must be maintained at all times.Post-approval CMC ensures patient safety and product reliability.It supports continuous improvement without compromising quality.Effective communication with regulatory authorities is essential.CMC post-approval is a dynamic and ongoing regulatory process.

CMC ⟹ CHEMISTRY MANUFACTURING & CONTROL

INTRODUCTION

CMS regulatory affairs is a specific area with RA that has usemate responsibility for providing CMC regulatory leadership and strategy required to active regulatory approvals

CMC RA provide knowledge,understanding,interpretation and utilization of regulatory guidance and regulations as well as industry and gov agency best practice and trends

EXAMPLE > CMC regulatory submission may contain information associated with API and the finish dosage form

Post approval regulatory affairs

The FDA may require a post approval study at the time approval of a premarket approval,humanitarian , device exemption or product development protocol application to help assure continued safety an effectiveness of the approved drug product of medical device

⇩

The safety surveillance is designed to detect any rare or long term advers effects over the much larger population and longer period

⇩

Harmful effects show in this trail may result in drug ban or restricted in certain usages

REGULATION FOR COMBINATION PRODUCTS AND MEDICAL DEVICES

A combination is product composed of any combination of a drug and a device ; A biological product and a device; a drug and a biological product:or a drug device and a biological product

Example>

1)monoclonal antibody combined with therapeutic drug

2) Device coated or impregnated with a drug or biological

3)prefilled drug delivery system

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MEDICAL DEVICES

Are instrument apparatus ,implement,machine,contrivance,implant, in vitro reagent or the other similar or related article including and component, part,or accessory

Medical device does not achives its primary intended purpose through chemical action within or on the body of Man or other animals and which is not depent upon beings metabolized for the achievement of its primary intended purpose

IN US,FDA has 3 assigned centers for regulation

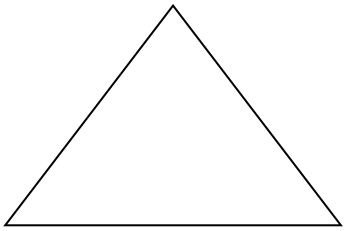
1) Center for drug evaluation and research
2) Center for device and radiological health
3) Center for biologics evaluation and research

Example
1)wound dressing with antimicrobial typically a device
CTD and ECTD FORMAT
CTD was agreed in nov2000 in san diego.usa
>IT provides for a harmonized structure and format for new product application
> CTD is maintained by the ICH of technical requirement for resgistaton of pharmaceuticals for human use

FDA CHARACTERIZED THE CTD

An information package of clinical, non clinical , manufacturing ,technical data in the same format and with the same content that would be submitted for registering new drugs in all three ICH region I.e US, European union and japan

CTD TRIANGLE Mod 1



Mod 2 mommmmod mod 3
Mod 4- mod 5
Mod 1; regional admining
Mod2; Qulality overall summary
Mod3;Quality
Mod4;Non clinical study report
Mod5; clinical report

ECTD>ELECTRONIC COMMON TECHNICAL DOCUMENTS

>ECTD composed of two type of specification
.)content specification as defined by ICH
.)Technical specification –electronic softwers.
>CTD-TOC
>Ectod –xml backbone

CHARACTERISTICS

>Structure
>All mod 1 to 5 have granularity options
>Pdf documents linked via Xml backbone
>Increase documents granularity
>Transparency of entire submission
>Ease of navigation and review

BENEFITS

- Can reduce time to approval
- Improved handling and archiving of submission
- Search functionality and increase tracking ability
- Allows for repurposing of DOCS for submission in other regions
- Accessibility to documents across modules
- Improve review efficiency

INDUSTRY AND FDA LIOISON

Experienced drug regulatory affairs personal are essential in the process of new development

- They are largely responsible for establishing a liaison with there counterparts at the US food and drug administration and other regulatory agencies globally

- FDA is one of our nation oldes consumer protection agencies dating back to 1862

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FDA STRUCTURE

NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH

CENTER FOR VETERNIARY DEVICES

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

CENTER FOR BIOLOGICS EVALVATION AND RESEARCH

CENTER FOR DRUG EVALUATION AND RESEARCH

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

U.S AND FDA

The U.S FDA is an agency of the u.s department of health and human services that is responsible for safety regulation of

- Most type of food
- Vaccine
- Drugs
- B.products
- Dietary supplement
- Biological medical product
- Cosmetics

2) The fda also enforces other notably sec 361 of the phs…act and associated regulations many of which are not directey related to food or drugs

3) The FDA has its head guarters at white oak,Maryland. The agency also has 233 field offices and 13 laboratories located throughout 50 states

GUIDELINEOF ICH Q.S.E.M

The international conference of harmonization of technical requirement for registration of pharmaceuticals for human use

- QUALITY (Q1 –Q10)

CHEMICAL & PHARMACEUTICAL QA

- SAFETY (S1-S10)

DEALING WITH VITRO & VIVO PRE CLINICAL TESTING

- EFFICACY(E1-E16)

CLINICAL STUDIES IN HUMAN BEINGS

- MULTIDISCIPLINARY (M1-M8)

TERMINOLOGY,ELECTRO STANDARDS COMMON

QUALITY

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Harmonization achievements in the quality area include pivotal-milestones such as the conduct of stability studies,approach to pharmaceutics quality an good manu-facturing practices

Q1> STABILITY
Q2>ANALYTICAL VALIDATION
Q3>IMPURTIES
Q4>PHARMACOPOEIAS
Q5>QUALITY OF BIO TECHNOLOGICAL
Q6>SPECIFICATION
Q7>GMP
Q8>PHARMACEUTICAL DEVELOPMENT
Q9>QRM
Q10>PHARMACEUTICAL QUALITY SAFETY

SAFETY

ICH has produced a comprechensive set of safety guidelines to uncover potential risks like carcinogenicity-genotoxicity and reprotoxity

S1>CARCINOGENCITY STUDIES
S2-GENOTOXICITY STUDIES
S3-TOXICOKINETICS AND PHARMACOKINETICS
S4-TOXICITY TESTING
$S_{5.}$ REPRODUCTIVE TOXICOLOGY
S6-BIOTECHNOLOGICAL PRODUCTS
S7-PHARMACOLOGY STUDIES
S8-IMMUNOTOXICOLOGY STUDIES
S9-NON CLINICAL EVALUATION FOR ANTICANCER PHARMACEUTICALS
S10-PHOTOSAFETY EVALUATION

EFFICACY

THE work carried out by ich under the efficacy heading is concerned with the design,conduct,safety and reporting of clinical trials

E1-E2-CLINICAL SAFETY
E3-CLINICAL STUDY REPORT
E4-DOSE RESPONSE
E5-ETHNIC FACTORS
E6-GOOD CLINICAL PRACTICE
E7-E11-CLINICAL TRIALS
E12-E13-GUIDELINES FOR CLINICAL EVALUATION
E14-CLINICAL EVALUATION
E15-16-PHARMACOGENOMICS

MUTIDISCILPLINARY

Those are the cross cutting topics which do not fit uniquely into one of the Q,S.E categories it includes the ICH medical terminology

M1-Med.DRA TERMINOLOGY\
M2-ELECTRONIC STANDARSDS
M3-NON CLINICAL SAFETY STUDIES
M4-CTD
MS-DATA ELEMENTS & STANDARD FOR DRUG DICTONARIES
M6-GENE THERAPHY
M7-GENOTOXIC IMPURTIES
M8-ECTD

REGULATORY REQUIREMENTS OF EU,MHRA,TGA AND ROW COUNTRIES

EU> EUROPRAN UNION

European medicines agency is a decentralized agency of the European union

- Established under the name in 1992 by the treaty on European union
- The agency is responsible for the scientific evaluation supervision and safety monitoring of medicine developed by pharmaceutical companies for the use in European

Market Authorization

To protect public health and ensure the availability of high quality,safe and effective medicine for europran citizens all medicines must be authorized before they can be placed on the market in the EU

Role of EMA

The European commission can also take action concerning other aspects of medicine regulation

- Right of initative-it can propose new or amended legislation for the pharmaceutical sector
- Implementation-it can adopt implementing measures as well as oversee the corret application of EU

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Guidelines

- EMA prepare scientific guidelines in cooperation with experts from its scientific committees and working groups
- These guidelines reflect the latest thinking on developments in bio-medical store

Authorization and supervision of mamufacturing

Manu-facturs,impartes and distributor of medicines in the EU must be licensed before they can carry out those activites

Clinical trials

The European clinical trials database tracts which clinical trials have been authorized in the EU .it is used by NCAs and clinical trial sponsors to enters information protocols and results of clinical trials

MHRA

Medical and healthcare products regulatory agency an executive agency of department of health of united kingdom
>MHRA was set up april 2003 bringing together the function of MCA and MDA
>MHRA is responsible for ensuring that medicines devices work,and are acceptably safe

ROLES

>LICENSING
-CLINICAL TRIAL LICENCE
-MANUFACTURING AND DEATER LICENCE
-SAFETY AND EFFICACY MONITORING
-ENFORCEMENT OF LAW
-REGULATION OF CLINICAL TRIALS
-PROVIDIND INFORMATION TO PUBLIC AND HEALTH PROFESSION

LICENSING PROCESS

-Application of clinical trial
-evaluation by MHRA
- Satisfies,doesn't satisfies
-clinical trials
-clinical trials results

MARKETING AUTHORIZATION

1)Centralized procedure
2)National procedure
3) Decentralized procedure
4) Mutal recognitation procedure

RENEWAL OF LICENSE

Application for renewal should be submitted at least six months before expiry
-New MAs
-Re-evaluations

- **TGA**

Therapeutic good administration is the regulatory body for therapeutics good in Australia

Objectives

Therapeutics good act 1989 which come into effect on 15feb1991 is to provide a national framework of regulation of therapeutics goods in Australia to ensure quality, safety, and efficacy of medicines

Regulatory frame work

1) Products are evaluated by the TGA For Q,S,E under the provision of sec.25 of therapeutic goods act 1989
2) Product in category include

>product included in schrdules of phm.benefits
>product that make therapeutic claims other than sun screening

Elements to regulate

>licensing and audit of manufacture
>pre-market assessment
>Post market regulatory authority

- **ROW COUNTRIES**

Means a country which is not included in the major market countries row means all the non major market countries

Key function

-product registration
-regulation of drug manufacturing,importation and distribution
-adverse drugs reaction monitoring
-licensing of promise

Registration

-Administactive documents
-API DMF open part

INDIA REGULATORY BODIES

-CDSC0
-MHFW
-ICMR
-IPA
-DTAB
-CDTL
-IPC
-NPPA

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