JGTPS, 2015, Vol. 6(3): 2777 - 2783

ISSN- 2230-7346

Journal of Global Trends in Pharmaceutical Sciences

Journal home page: www.jgtps.com

MEDICATED DEVICE COMBINATION PRODUCT: AN OVERVIEW

Vikash Kumar Vyas,
Jignesh S. Shah,
Dilip Maheshwari

Department of Quality Assurance and Pharm Regulatory Affairs, L. J. Institute of Pharmacy, Ahmedabad-382210, Gujarat, India

ABSTRACT

In the current scenario more and more development in science and technology had led to the new technology or innovation in the healthcare system, so these advances had led to the existence of Medicated Device Combination Products. Medicated Device Combination Product is Combination of drug and Medical Device which are new and advanced technology for improving patient compliance and minimize the risk of infection cause by Medical Device. In order to tackle the clinical problems of the future, Medicated Device Combination Product will be combined these are emerging and morden day techniques for the drug delivery Products. In this article we describe the Medicated Device Combination Product in USA, Europe and Canada and their advantage over Medical Device and local drug therapy, Clinical trial requirement, current market scenario as well as future market trend.

Keywords: Medicated Device Combination Product, Medical Device, USA, Europe, Canada

INTRODUCTION

Medicated Device Combination Product is Combination of Medical Device and drug that are physically and chemically combined and produce a single entity. These Products having great potential as they combine the effect of a drug with Medical Device thus create a new type of technology way to use Product; like orthopedic implants with antibiotics which increase the stability of implants by preventing any infection. These types of Product are very much in demands in these days for localized drug delivery in cancer patient in which more drugs can reach at cancer site and produce more therapeutic effectiveness.

Address for correspondence

Dr. Jignesh S. Shah*
Department of Quality Assurance and Pharm Regulatory Affairs, L. J. Institute of Pharmacy, Ahmedabad-382210, Gujarat, India
E-mail: jss192@gmail.com

Medicated Device Combination Products are increasingly being developed to enhance the safety and effectiveness of conventional Medical Products and Medical Device. For example drug eluting cardiovascular stent may reduce the need of repeated surgery by preventing of restenosis that may arise or occur after stent implants.

Fig.1 Schematic representation of the assembly of Combination Products: A drug (in Red) is integrated into a Device system (in blue)

MEDICAL DEVICE [1]

A Medical Device is an instrument, apparatus, implant, in vitro reagent, or similar or related article that is used to diagnose, prevent, or treat disease or other conditions, and does not achieve its purposes through chemical action within or on the body

MEDICAL DEVICE AS PER USA [1]

A Medical Device is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part or accessory which is:

- Recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,

- Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

Classification:

- Class I: simple, low-risk Devices(elastic bandages, examination gloves, and handheld surgical instruments)
- Class II: more complex, higher risk(monitoring Devices, infusion pumps, surgical drapes, and powered wheelchairs)
- Class III: most complex, highest risk (angioplasty catheters, defibrillators, replacement heart valves, and neurostimulators for use in the brain.)

MEDICAL DEVICE AS PER EUROPE [1] [2]

Any instrument, appliance, material, apparatus, software, or other article, wheather it is used alone or in combination together with any accessories including the software intended by manufacturer to be used specifically for therapeutic or diagnostic purpose and essential for medical device proper application, intended by the manufacturer to be used for human beings for the purpose of:

- Diagnosis, monitoring, treatment, prevention or alleviation of disease
- Diagnosis, treatment, alleviation of, or compensation for an injury or handicap, monitoring
- Investigation, replacement or modification of the anatomy or of a physiological process
- Control of conception

Classification

- Class I - generally regarded as low risk
- Class IIa - generally regarded as medium risk
- Class IIb - generally regarded as medium risk
- Class III - generally regarded as high risk

MEDICATED DEVICE COMBINATION PRODUCT [3]

The concept of regulation for Medicated Device Products evolved in USA in 1990, when the Safe Medical Device Act of 1990 (SMDA) passed, by making an amendment in the Federal Food, Drug and Cosmetic Act (FFD&C). In 1991, the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), and the Center for Devices and Radiological Health (CDRH), entered into three Inter-center Agreements (ICAs). The ICAs continue to provide helpful guidance related to Product regulation the body of regulatory decisions has grown and over time, the ICAs have become incomplete statements. FDA issued a final rule in 1991 establishing the procedures (the request for designation, RFD, process) for determining the assignment of Medicated Device Combination Products under part III. That time need a statutory regulatory authority so USFDA assigned in 2002 Office of Combination Products (OCP) was established as required by the Medical Device User Fee and Modernization Act (MDUFMA) of 2002. Although these types of Products are used in other countries, these Products are not officially defined as Medicated Device Combination Products or some different designation which followed only for this kind of Products and hence regulated differently in various countries.

USA [4]

Medicated device Combination Products are defined in 21 CFR 3.2(e). The term medicated device Combination Product includes:

1. A Product comprised of two or more regulated components, i.e. drug/Device, biologic/Device, drug/biologic, or drug/Device/biologic, that are physically, chemically, or combined or mixed and produced as a single entity;
2. Two or more separate Products packaged together in a single package or as a unit and comprised of drug and medical Device Products, medical Device and biological Products, or biological and drug Products;
3. A drug, medical Device, or biological Product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, medical Device, or biological Product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed Product the labeling of the approved Product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or
4. Any investigational drug, medical Device, or biological Product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, Device, or biological Product where both are required to achieve the intended use, indication, or effect.

Tab.1 example of Combination Product as per USA

Definition	Examples of Combination Product
21 CFR 3.2 (e) (1)	• Monoclonal antibody combined with a therapeutic drug. • Device coated with drug or biologic: Drug eluting stent and Catheter with antimicrobial coating • Condom with spermicidal and Orthopedic implants with growth factor • Prefilled syringe, insulin injector pen, and metered dose inhaler.
21 CFR 3.2 (e) (2)	• Drug and biological Product package with a delivery Device. • Surgical tray with surgical instruments, drapes, lidocaine or alcohol swabs.
21 CFR 3.2(e) (3) Or (e) (4)	• Photosensitizing drug and activating laser/ light source. • Iontophoretic drug delivery patch and Controller

EUROPE [2]

The definitions of Medicated Device Combination Products represent rather two basic two-tiered approaches, drug delivery Devices and Devices incorporating drug substances with ancillary action, leading to two types of medicated device Combination Products and three possible regulatory authorization pathways. In Directive 93/42/EEC. It is stated in; • Art. 1(3) for Medical Devices intended to administer a drug Product that the Medical Device shall be governed by the present Directive, however, such a Medical Device and the drug Product form a single integral Product which is intended exclusively for use in given Combination and which is not reusable, that single Product shall be governed by Directive 2001/83/EC. In Art. 1(4) Where a Medical Device incorporates, as an integral part, a substance which, if used separately, may be considered to be a drug Product within the meaning of Article 1 of Directive 2001/83/EC and which is liable to act upon the body with action ancillary to that of the Device, that Device must be assessed and authorized in accordance with this Directive.

Tab.2 Example of Medicated Device Combination Product as per Europe

Category	Examples of Combination Product
Art.3 of Dir.93/42/EEC drug delivery system	1. Implantable infusion pump, 2. Nebulizer, 3. Prefilled syringe, jet injector,
Art. 3 of Dir. 93/42/EEC Medical Device and drug Product from a single integral Product	1. Aerosol containing medicinal Product, 2. Nebulizer precharged with a specific medicinal Product, 3. Plastic beads containing antibiotic, 4. Wound dressing containing an antimicrobial agent,
Art. 4 of Dir. 93/42/EEC Medical Device containing medicinal substance with ancillary action	1. Catheters coated with heparin, 2. Drug eluting stent, 3. Bone cement containing antibiotic, 4. Condoms coated with spermicides, 5. Haemostatic Devices with collagen.

CANADA [5]

Is a therapeutic Product that combines a drug component and a Medical Device component (which by themselves would be classified as a drug or a Device), such that the distinctive nature of the drug component and Medical Device component is integrated in a singular Product.

Tab.3 Example of Medicated Device Combination Product as per Canada

Category	Examples of Combination Product
Combination Products that have been classified as drugs:	• prefilled syringes • patches for transdermal drug delivery
Combination Products that have been classified as Devices:	• drug eluting stent • bone cement with antibiotic • antimicrobial catheter • blood bags with anticoagulant
Combinations of drugs and Devices to which this policy does not apply and which must comply with both the Food and Drug Regulations and the Medical Devices Regulations	• epidural tray containing drugs and Devices • first aid kit containing a drugs and Devices
Products for which neither set of regulations apply	• minimally manipulated tissue

Tab. 4 Difference between Medical Device and Medicated Device [6] [7]

S. No.	Medicated Device	Medical Device
1.	It is Combination of drug and Device or Device and biologics or drug/Device/biologics	It is single unit Product
2.	It produce therapeutic action with the help of drug	It not produce therapeutic effect
3.	Medicated Device is composition of chemically and physically	It is physical unit not provide chemical action
4.	Medicated Device is targeted drug delivery system	Medical Device is not used in targeted drug delivery system
5.	Medicated Device is regulated by office of Combination Product(OCP) with the help of intercenter agreement between OCP and CBER, CDRH, CDER in united state of America	Medical Device is regulated by CDRH in united state of America.
6.	It minimize the risk of infection by Medical Device	It will be produce infection at the site of drug delivery

MEDICATED DEVICE HOW TO SUPERIOR FROM MEDICAL DEVICE AND DRUG [8]

Advantages of Medicated drug release strategies over systemic drug therapy

1. Lower dose required for treatment
2. Greater control over toxicity and bioavailability of drug dose
3. Less susceptibility to build up antibiotic resistance
4. Extended duration of drug release
5. Possibilities to combine local and systemic drugs with different Kinetics
6. Controlled release from surfaces of Combination Devices directly to site of action
7. Avoid of systemic drug exposure
8. Direct mitigation of Medical Device-centered infection using Combination Device release
9. Drive to improve existing Device
10. Medical Device function can be enhance by including a therapeutic agent

CURRENT MARKET OF MEDICATED DEVICE COMBINATION PRODUCT [9]

It was estimated that Medicated Device Combination Products market is increased from approximately US$6 billion in 2004 to nearly $10 billion by 2009. Furthermore, the total global value of the Medicated Device Combination Products market is increases to $11.5 billion in 2010. Currently, the market has a potential of US$20.6 billion and has been experiencing a growth of 15% CAGR for the past two years. In the next five years, the market is expected to grow at a CAGR of 11.8%. Global Medicated Device Combination Products market expected to grow to $115.1b in 2019.

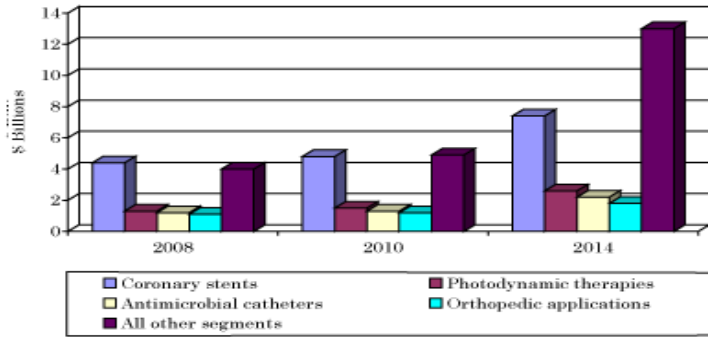

Fig. 2 Sales of Medicated Device Combination Product (2008-2014)

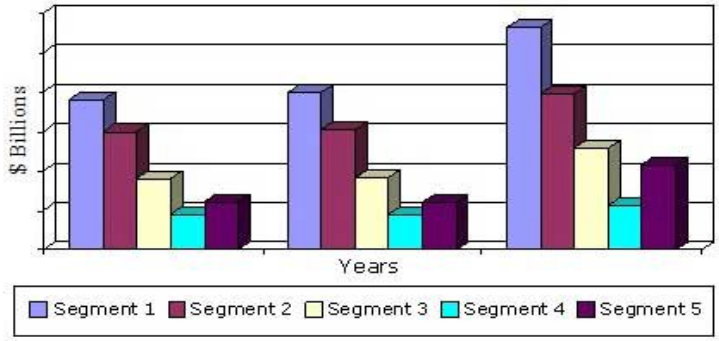

Fig.3 Sales of Medicated Device Combination Product (2013-2019)

REGULATORY AGENCY OF MEDICATED DEVICE COMBINATION PRODUCT [1]

Medicated Device Combination Product regulated by following agencies given at table 5.

Country	Regulatory Agency
USA	OCP CDRH CDER CBER
EUROPE	Consider primary mode of action. Opinions must be sought from relevant expert committees for certain Combination Products
CANADA	MDB – when classified as a Device.

PRE-CLINICAL SAFETY STUDIES [10]

1. The design of preclinical studies varies by the type of Product studied and the data that will ultimately need to be included in an IND or IDE.
2. Sponsors can also obtain insight into study design by reviewing approval documentation for approved Medicated Device Combination Products
3. FDA considers the entire Medicated Device Combination Product in assessing the data required to support the Product submission, so the type of clinical data needed will be affected by the parts of the Product that requires clinical data to support marketing approval.
4. For some new Medicated Device Combination Products, the clinical data may need to support the entire Combination Product, particularly when the Product's efficacy claims relate to both constituent parts and when the Product is highly integrated.

CLINICAL TRIAL OF MEDICATED DEVICE COMBINATION PRODUCT [11]

The clinical trial of Medicated Device is done in three steps- BA/BE Study, Pilot study, Pivotal Studies

BA/BE Study:

BA/BE studies typically must be randomized, placebo-controlled and parallel in design and require comparative clinical endpoints in patients with a clinical diagnosis for the condition of interest

In such trial investigator randomize patients to receive Medicated Combination Product, reference Product alone or the Device alone. Randomization typically 2:2:1 with equal number randomized to each active treatment arm and half as many to

Device alone arm. If any ethical issue concern FDA allow a crossover design for the study

The FDA does not specify the size of the required BA/BE studies. It is the sponsor's responsibility to enroll sufficient patients for the study to demonstrate bioequivalence between the Products FDA guidance documents for clinical evaluation of such Products specify that each study should contain a minimum of 100 subjects

Pilot study:

Usually about 20 patients, to establish safety, begin to define the expected adverse effects and validate the performance of the Product in the field before advancing to the second step of a pilot study. Smaller, pilot controlled trial, generally involving about 50 to 60 patients, verifies safety, and confirms patient inclusion/exclusion criteria before moving to the larger pivotal trial.

Pivotal Studies:

a randomized, double-blind two-arm study of a new drug- or biologic-coated Device against a non-coated Device would be used to show non-inferiority in efficacy with an increase in safety, such as fewer adverse events, or decreased infection rates. Such a trial typically requires about 1,500 patients, equally randomized to the two arms. In contrast, a two or three-arm superiority trial against the competitor predicate' Product increases trial size significantly, typically to 3,000 to 5,000 patients, while also increasing trial complexity, number of sites required and duration. The FDA generally only requires Combination Products trials to show 'substantial equivalence' to a predicate Device or standard of care, so the patient numbers are generally smaller in these trials. In contrast, Centers for Medicare & Medicaid Services (CMS) may require a new Combination Product be superior in terms of safety, efficacy or both, with a decrease in the overall cost of care, before a new reimbursement code can be issued.

It may be appropriate to conduct studies to evaluate the following potential risks[6]

- Leachable/extractable of the Device materials into the Drug/biologic substance or final Medicated Device Combination Product
- Changes in stability of the Drug constituent when delivered by the Medical Device or when used as a coating on the Medical Device.
- Drug adhesion/absorption to the Medical Device materials that could change the delivered dose.
- Presence of inactive breakdown Products or manufacturing residues from Medical Device manufacture that may affect safety, or Medical Device actions that could change the Drug performance characteristics at the time of use.
- Change in the stability or activity of a Drug constituent when used together with an energy emitting Medical Device.
- The material properties of a delivery Cather may be adversely affected by Drug/biologic Products.

Other possible requirement for development of a Medicated Device Combination Product [6]

- In vivo pharmacokinetic studies may be necessary to assess changes in formulation, strength, route of administration, dosing, population or other factors that may alter the extent or time course of systemic exposure. These studies might be used to determine Drug release kinetics such as release rate, local peak concentrations of the Drug, local distribution and systemic bioavailability C_{max}, T_{max}, etc.
- Dose ranging or dose finding studies in humans may be appropriate to determine dose adjustments for safety/effectiveness when therapy is targeted to a local site.
- Acute and repeat dose toxicity studies using the new route of administration may be appropriate to determine the NOAEL (no observed adverse effect level) and toxicity profile of the Combination Product. Typically, these studies would evaluate the intended clinical formulation and dosing regimen/frequency that will closely approximate its use in clinical settings
- Special safety studies may be appropriate for certain patient populations e.g., hepatotoxicity, QT prolongation, special populations.
- Specific safety monitoring in the clinical study may be appropriate to obtain data on the novel aspects presented by the Combination Product; e.g., local toxicity for a new route of administration.

CONCLUSION:

Medicated Device Combination Product is the future of pharmaceutical industry. This article gives an overview about the Medicated Combination Product, and global market trend regarding Medicated Device Combination Product. Medicated Device Combination Product creates new type of industries as well as established collaboration between pharmaceutical industries and Medical Device industries

ACKNOWLEDGEMENT:

The authors are thankful to Dr. K. Pundarikakshudu, Principal of L. J. Institute of Pharmacy, Ahmedabad, India for providing all the facilities to carry out the work.

REFERENCES:

1. wikipedia.org/wiki/Medical_Device#Definition_in_United_States_by_the_Food_and_Drug_Administration.html
2. Narechania Siddharth N*, Trupesh Pethani, Dr. Navin.R.Sheth "a review on comparison of regulatory requirements to approved drug Device Combination Products in Europe AND USA" World Journal of Pharmacy and Pharmaceutical Sciences 2014, 3(6), 455-475
3. http://dash.harvard.edu/handle/1/8852096
4. http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm118332.htm
5. http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/applicdemande/pol/combo_mixte_pol_2006-eng.pdf
6. Kothavihar, elphine prabahar, "Regulatory strategy for registration of Combination Products to us-fda" International Journal of Drug Regulatory Affairs; 2014, 2(3), 27-42
7. J. Vijay Dwarka, S.G. Vasanthraju, Latif Jamadar, and N. Udupu "Combinational Product: A Regulatory Review" International Journal of Pharmaceutical Science Review and Research 2010, 5(1), 52-60
8. Peng Wu, David W. Grainger "Drug/Device Combinations for local drug therapies and infection prophylaxis" ELSEVIER Biomaterials 27 (2006) 2450–2467
9. http://www.bccresearch.com/market-research/pharmaceuticals/drug-Device-Combinations-markets-report-phm045d.html
10. Shah Binal B, Patel P M, Patel N.M "Regulatory Requirements Of Combinational Products: An Overview (USFDA)" International Journal of Pharmaceutical & Biological Archives 2011, 2(3),822-827
11. http://novellaclinical.com/content/uploads/2014/08/MedDev-Regulatory-Road-Combination-Products-Novella-Clinical-White-Paper.pdf

How to cite this article:
Vikash Kumar Vyas, Jignesh S. Shah, Dilip Maheshwari, Medicated device combination product: An over view, 6 (3): 2777 – 2783 (2015)