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# Comprehensive Study Of Regulatory Requirement For Product Development And Quality Consideration Guidelines Of Tds In Us And Eu.

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## Abstract

This thesis covers initial variant submissions for transdermal patches intended for systemicdistribution as well as new marketing authorization applications (including generic or abbreviated applications).

There is guidance on the standards of quality for transdermal patch development, manufacture, excipient characterization, drug product control, packaging, and stability. In vitro performance testing is examined in particular with regard to drug release, adhesion, andskin permeability, as well as its relationship to clinical and in vivo performance.

Along with the Guideline on the Pharmacokinetic and Clinical Evaluation of Modified-Release Dosage Forms, it should be read.

Transdermal patches are made to distribute the active substance(s) via the skin in a regulated manner, primarily by diffusion, with a certain pace and amount of systemic absorption.

## Introduction:

### Medical device

Definition of medical device as per WHO a device, instrument, apparatus, or machine used inthe detection, measurement, restoration, correction, or modification of the structure or function of the body for some health purpose, or in the prevention, diagnosis, or treatment of illness or disease. Typically, pharmacological, immunological, or metabolic methods are not used to accomplish the goal of a medical device.[1]

Medical device is defined as “any instrument, machine, contrivance, implant, in vitro reagentthat's intended

to treat, cure, prevent, mitigate, diagnose disease in man". [2]

According to FDA medical device is an apparatus, implement machine, appliance, implantreagent for in vitro use software material or other similar or related article intended by manufacture to be used alone or in combination for human beings for one or more of the specific medical purpose:

-Diagnosis, prevention, monitoring treatment or alleviation of disease

-Diagnosis, monitoring treatment or alleviation of disease or compensation for an injury

- Investigation replacement modification or support of the anatomy or if physiologicalprocess;

-Supporting or sustaining life

-Control of conception

-Disinfection of medical device [3]

Any object designed for use in medicine is considered a medical device. Utilizing a device for medical purposes carries a large risk of risks, hence medical devices must be demonstrated to be safe and effective with a fair degree of assurance before governing governments permit the sale of the device in their nation. In general, the quantity of testing needed to verify a device's safety and efficacy increases as the associated risk does.

Additionally, if related risk rises, the patient's potential benefit must rise as well.

Medical devices weren't governed in the US until the 1938 passage of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The Medical Device Amendments to the FD&C Act, which were passed later in 1976, established medical device regulation and oversight in the United States as we know it today. The Medical Device Directive, which is a group of relatedlaws, established the current system of medical device regulation in Europe in 1993. (MDD).The MDD was replaced by the Medical Device Regulation (MDR) on May 26, 2017.

Both the intended application and the indications for usage of medical devices differ. Simple,low-risk examples include tongue depressors, medical thermometers, disposable gloves, and bedpans, whereas complex, high-risk examples include implantable devices that support life.The use of pacemakers and other embedded software-enabled devices for medical diagnostics, implants, and prosthetics is an example of a high-risk device. A significant area of the study of biomedical engineering is the design of medical equipment. **(4)**

## Medical Device Classification:

| CLASS | RISK | EXAMPLE |
|---|---|---|
| Class-I | Low Risk | Tongue Depressor |
| Class-II | Medium Risk | Pregnancy Test Kits |
| Class-III | High Risk | Heart Pacemakers |

**Table 1. classification in the US** [8]

| CLASS | RISK | EXAMPLE |
|---|---|---|
| Class-I | Low Risk | Tongue Depressor |
| Class-II | Medium Risk | Sterile surgical gloves |
| Class-III | Medium to High Risk | Surgical lasers |
| Class-IV | High Risk | Absorbable surgical sutures |

**Table 2. classification in the EU** [5,6,7]

## Introduction to Transdermal Patches:

A transdermal patch, also known as a skin patch, is an adhesive patch applied to the skin that contains medication that is intended to be absorbed into the bloodstream through the skin.[6] The term "transdermal therapeutic systems" refers to self-contained, self-discrete dosage forms that, when applied to undamaged skin, distribute the drug to the systemic circulation ata controlled rate.[7]

There has been a transdermal drugs delivery technology for a very long time. The most widely used systems for dermatological problems in the past were topically administered lotions and ointments. Systemic side effects are common with some of these formulations, which is an indication of skin absorption. Several medications have been rubbed on the skinas systemic treatments. The phrase "transdermal delivery system" broadly refers to any medicine formulation applied topically with the goal of releasing the active component intothe bloodstream.

Transdermal therapy systems have been created to offer controlled continuous drug administration to the systemic circulation through the skin. Additionally, it overcomes a number of negative effects include painful drug delivery and the medication's first pass metabolism that occurs when using alternative drug delivery systems. Therefore, there has been a lot of interest in this transdermal drug delivery system recently. Numerous medications that can be injected directly into the bloodstream through the skin have been developed. The medication is painless, and the regulated drug release is one of the system's key benefits. A transdermal patch that clings to the skin is primarily used to administer the medication to the skin. A transdermal patch contains a number of parts, such as liners, adherents, drug reservoirs, drug release membrane, etc. that are essential for the medication'srelease through the skin. To distribute the medicine from the transdermal patch, many types of patches and application techniques have been developed. Due to its

many benefits, it has emerged as one of the most actively researched areas among the numerous drug delivery systems.

An alternative method of medication administration is offered by a transdermal drug deliverydevice, which can have either an active or passive design. Pharmaceuticals can now be givenacross the skin barrier thanks to these devices. Transdermal patches operate quite simple in theory. The inside of a patch, which is worn on the skin for a prolonged period of time, receives a relatively high dosage of a medicine. The medicine directly enters the bloodstreamthrough the skin through a diffusion process. The medication will continue to diffuse into theblood for a considerable amount of time, maintaining the consistent concentration of drug in the blood flow, due to the high concentration on the patch and low concentration in the blood [8].

## BACKGROUND

The skin's primary job is to shield the body from the outside environment, and it typically serves as a very effective barrier against the penetration of active chemicals. Passive diffusioncan nevertheless produce a therapeutic effect for some active compounds, depending on their physicochemical characteristics.

Otherwise, permeation enhancement, which entails the alteration of the formulation by one ofthe following:

-Increasing the active ingredient's thermodynamic activity during formulation (for example,through super saturation)

-Passive penetration enhancement (for example, prodrugs, nan carriers, micro emulsions, andliposomes can act as carriers for the active ingredient)

Physical methods including iontophoresis, micro oration, sonophoresis, and microdermabrasion, which may be defined as active augmentation strategies, can alsoimprove permeation.

A flexible, multi-layered, pharmacological single dose preparation of varied size containing one or more active substances to be placed to the intact skin for systemic absorption is knownas a transdermal patch, also known as a transdermal drug delivery system (TDDS). Pressure- sensitive adhesives are typically used in this formulation to ensure the preparation's adherence to the skin. A backing sheet that is generally impervious to water and impermeableto the active ingredient is included in a transdermal patch. Before placing the patch to the skin, the protective liner covering the patch's releasing surface must be peeled off.

Transdermal patches are made to slowly release the active ingredient(s) through the undamaged skin, producing a prolonged and suitably steady rate of systemic absorption. Therate-limiting phase for the active substance's systemic absorption is typically cutaneous absorption. As an alternative, the active ingredient might be mixed with or dissolved in a(semi-solid) reservoir with a membrane controlling the release and diffusion of the activeingredient(s) from the patch. The transdermal patch can also be designed using both drugdelivery theories as a way to regulate drug delivery to the skin's surface. [9]

**Review of Literature**

1. Patel, D.S., Patel, M.V., Patel, K.N., Patel, B.A., Patel, P.A: The effectiveness of around 70% of the medications used today, which are taken orally, is determined to be subpar. Transdermal medication delivery systems were developed to enhance such features. Transdermal drug delivery system (TDDS), which varies from conventional topical drug administration, offers a way to prolong medication release while also reducing the strength of action and, thus, reducing the adverse effects connected with its oral therapy. The administration of the drug's active components through the skin is known as a transdermal drug delivery system. [17]
2. Kajal Sahu: A transdermal patch is a medicated adhesive patch applied to the skin in order to trans dermally deliver a specific dose of medication into the bloodstream. This frequently encourages the healing of a body part that has been hurt. The fact that the patch offers a controlled release of the medication into the patient over other medication delivery methods like oral, topical, intravenous, intramuscular, etc. is a benefit of transdermal drug delivery. Typically, this is accomplished by either a porous membrane covering a reservoir ofmedication or by body heat melting thin layers of medication embedded in the adhesive.[18]
3. Patel, D.S. , Patel, M.V. , Patel, K.N. , Patel, B.A. , Patel, P.A : The effectiveness of around 70% of the medications used today, which are taken orally, is determined to be subpar. Transdermal medication delivery systems were developed to enhance such features. Transdermal drug delivery system (TDDS), which varies from conventional topical drug administration, offers a way to prolong medication release while also reducing the strength of action and, thus, reducing the adverse effects connected with its oral therapy. The administration of the drug's active components through the skin is known as a transdermal drug delivery system.[19]

Kajal Sahu: A transdermal patch is a medicated adhesive patch applied to the skin in order to transdermal deliver a specific dose of medication into the bloodstream. This frequently encourages the healing of a body part that has been hurt. The fact that the patch offers a controlled release of the medication into the patient over other medication deliverymethods like oral, topical, intravenous, intramuscular, etc. is a benefit of transdermal drug delivery. Typically, this is accomplished by either a porous membrane covering a reservoir ofmedication or by body heat melting thin layers of medication embedded in the adhesive. [20]

## AIM: Comprehensive Study of Regulatory Requirementfor Transdermal Patches in US and EU

## OBJECTIVE

- To understand the regulatory requirement of medical device for transdermal medicationdelivery systems in the US and EU.
- To know the basic knowledge about TDS.
- To study the pharmaceutical development and quality consideration for US. - To study the pharmaceutical development and quality consideration EU. - To understand the advantages and

disadvantages for TDS of US and EU.

## NEED OF STUDY

The primary goal of the study was to identify best practises for transdermal medication delivery systems in the US and EU.

The study discussed a specific document providing recommendations for pharmaceutical development and quality factors for transdermal drug delivery systems.

So the need of study is specifies the regulatory requirement of TDS for pharmaceutical development and quality consideration in US As well as pharmaceutical development and quality consideration in EU.

## PLAN OF WORK

1. Literature survey
2. Selection of topic
3. Selection of countries
4. Gathering information from articles & guidance documents
5. Analyse all data and arrange it in the proper format.
6. Discussion
7. Conclusion
8. References

## TDS PRODUCT DEVELOPMENT

The following section gives an overview of product and process development factors from a pharmaceutical development standpoint. As previously stated, the creation of a TDS product must also be in accordance with design controls (21 CFR part 93 820.30). We understand thatthe language used in 21 CFR part 820.30 may differ from that utilised in a specific pharmaceutical development programme. Applicants should be able to describe to FDA how the language they employ relates to design control principles and standards when pharmaceutical development techniques are leveraged and expanded upon to demonstrate compliance with design controls for a TDS product.

### A. Quality Target Product Profile

Prior to developing the TDS, the applicant should determine the intended quality target product profile (QTPP). The QTPP is a projected description of the TDS product's qualityfeatures that, ideally, will be reached to ensure the intended quality, taking into mind the product's safety and efficacy (ICH Q8(R2)). In general, QTPP aspects and quality considerations for TDS may include the following.

| QTPP Element | Quality Considerations |
|---|---|
| In vivo delivery of active ingredient to achieve therapeutic effect | Formulation design and manufacturing control |
| Minimization of residual drug | Formulation design |
| Adherence for duration of wear period | Excipient selection, component control, physicaldesign (shape, dimensions, etc.), and manufacturing control |
| Minimization of irritation | Formulation design |
| Chemical and physical stability for shelf life | Formulation design, container closure attributes, storage conditions |
| Non-drug substance-related impurities | Excipient selection and manufacturing control |

Table 3. Quality Target Product Profile

Other QTPP elements may exist depending on therapeutic need, patient population, or other functional property requirements. For example, the size of the finished product may be a

QTPP element depending on the location on the body where the product is to be applied or if the patient 1population is paediatric.

## B. Critical Quality Attributes

### 1. Product TDS

The applicant should establish a list of prospective CQAs early in the TDS development process. A CQA is a physical, chemical, biological, or microbiological property or feature that must be within an acceptable limit, range, or distribution to assure product quality (ICH Q8(R2)). The product QTPP, in conjunction with existing information, risk assessments, and/or experiments, can be used to produce a list of product CQAs. Each CQA should be related to one or more parts of the TDS product QTPP, either alone or in collaboration with one or more other CQAs. As product development develops and new knowledge is learned, the list of product CQAs might be changed. The application should also include the CQAs for the drug substance(s), excipients, components, and container closing mechanism.

CQAs for TDS are typically appearance (such as the absence of visible crystals), dimensions, dosage unit uniformity, assay, permeation enhancer content, impurities and degradants, in vitro drug release profile, preservative/antioxidant content (if present), peel adhesion, tack, release liner peel strength, shear strength, cold flow, residual solvents, residual monomers, microbial limits, and package integrity.

### 2. Drug Substance

The selection of a drug substance should be justified based on the drug substance's physicochemical and biological qualities, which might impact the performance of the TDS product and its manufacturability. Properties that affect the rate of delivery, such as molecular weight, melting point, partition coefficient, pKa, aqueous solubility, and pH, should be taken into account. Other drug substance properties, such as particle

size, crystal shape, and polymorphism, should be assessed and justified in terms of product performance.

### 3. Excipients and Component

Excipients and components utilised in TDS can include a variety of adhesives, permeationenhancers, rate regulating or non-rate controlling membranes, solubilizers, plasticizers/softeners, or tackifiers, all of which can impact TDS quality and performance.

Extensive certification of essential excipients and components is critical to ensuring optimumproduct quality attributes in transdermal and topical formulations, as well as facilitating the postapproval modification procedure for changes in raw materials, manufacturing method, orsuppliers.

For example, when qualifying the adhesives in a TDS product, an applicant should considerthe following attributes:

- For adhesive polymer(s) as raw material(s): molecular weight, polydispersity, spectroscopic analysis (e.g., infrared radiation (IR) absorption), thermal analysis, intrinsic orcomplex viscosity, and measurement of residual monomers, dimers, solvents, heavy metals, catalysts, and initiators.
- For adhesive as a laminate (in the absence of the active ingredient and other excipients):residual solvents, peel, tack, shear, and adhesion.
- For adhesive in the final product (along with drug substance and other excipients and components): identification, residual monomers, dimers, and solvents; impurities; loss on drying; and uniformity. Other properties to be considered include the viscoelastic properties(such as elastic modulus (G'), viscous modulus (G"), and creep compliance (J)), and functional properties including, but not limited to, peel, shear, adhesion, tack, in vitro drug release, and in vitro drug permeation.

The qualities of an adhesive as a raw material (e.g., rheology, including intrinsic viscosity and complex viscosity) might influence the quality attributes of the end product. Adhesive suppliers' criteria are frequently broad; as a result, adhesive raw material acquired throughoutthe product's life cycle may vary substantially within the adhesive providers' specifications. The rheological parameters of the adhesive lots utilized in the pivotal in vivo study for TDS, for example, may not be consistent with the supplier's previously manufactured adhesive lotsor future adhesive lots. As a result, applicants should acquire historical rheology values from the adhesive producer in order to better understand their process capabilities and the possibleimpact of adhesive variability. Contains Nonbinding Recommendations Rheology on the Draft — Not for Implementation.

### 4. Identifying Labelling

Applicants are encouraged to incorporate a representative label early in development to assure the labelling process or inks utilized for printing do not interact with the TDS product,and to properly assess inks during extractable and leachable studies. The identifying label is typically placed on the backing membrane of TDS and should, at minimum, include the product name and strength. Transdermal and topical systems that are clear, translucent, or colored to match human skin tones can make it difficult to find the TDS on the patient, and have led to medication administration errors when patients or caregivers fail to remove old systems and apply more than one system at a time. Clear or translucent TDS may also be difficult to find if they detach prematurely from a patient, thereby increasing the potential forsecondary or accidental exposure of the drug to a health care provider, caregiver, or child.

Therefore, we recommend the backing membrane be printed with ink that has adequatecontrast and remains visible for the duration of system wear and after disposal.

### C. Product and Process Development

To ensure TDS products have the identity and strength, as well as the quality and purity characteristics required by section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act,the principles of quality by design (QbD) and elements of pharmaceutical development discussed in ICH Q8(R2), Q9, and Q1013 should be applied throughout the TDS life cycle (FD&C Act). TDS can be as basic as a single medication dissolved in a single adhesive or as complicated as multi-component, multi-adhesive, multi-laminate matrices. TDS excipients and components can include a variety of adhesive systems, permeation enhancers, rate regulating or non-rate controlling membranes, solubilizers, plasticizers/softeners, and tackifiers.

As a general rule, product development strategies should strive to reduce product complexity while still meeting QTPP requirements. Less complicated items are more likely than more complex ones to have fewer possible failure mechanisms. As product complexity diminishes, product and process controls can be simplified, lowering the likelihood of manufacturing issues happening during ordinary commercial manufacture.

## 2. INFORMATION TO BE SUBMITTED IN AN APPLICATION

An applicant must include technical facts and information in sufficient detail to allow the Agency to make an informed decision regarding whether to accept the application or if grounds for refusal exist under sections 505(d)14 or 505(j)15 232 of the FD&C Act. Thiscontains data about the medication substance16 as well as data about the TDS product.

The sections that follow advise applicants on pharmaceutical development and quality information that should be included in the application sections outlined in ICH M4Q.

### A. Pharmaceutical Development

Section 3.2.P.2 of the application, as described in ICH M4Q, should contain information onstudies conducted to establish that the dosage form, formulation, manufacturing process, container closure system, microbiological attributes, and usage instructions specified in theapplication are appropriate for the TDS product's intended use. The following issues shouldbe addressed by the applicant:

- A description of the QTPP.

- A list of the CQAs of the TDS product, along with the limit, range, or distributionassociated with each CQA and appropriate justification.
- Identification of those aspects of the drug substance, excipients, container closure system, and manufacturing processes important to attaining product quality.

➢ In particular, the selection of excipients and components, their concentrations (asappropriate), and their functional characteristics affecting TDS performance should be discussed. For example, the applicant should describe the impact of penetration enhancers on the adhesive properties of the TDS, solubility of the drug substance in the blend, and skin permeation

- Applicants should specify the allowable ranges around the process parameters and material attributes that have a potential to impact TDS product CQAs withjustification and describe how they will be monitored
- A description of the quality risk assessments, potential failure modes, and product andprocess control strategies.

**1. Batch Formula**

Batch formulae for processes that utilise solvated raw materials should be designed to handlevariations in raw material solvent concentration. To account for evaporation during drying, drug substance overages and excipient excesses can be added to a batch, but the amount of overage or excess should be regulated and validated by process development studies. Cross- linking reactions should be described by applicants since they affect the chemical composition and quality of the end product.

**2. Expectations for Registration/Exhibit Batches**

Applicants shall provide data for registration/exhibit batches created from three unique laminates, each made with a different lot of medication ingredient, adhesives, backing, and/orother essential constituents in the TDS product. To show the robustness of the manufacturing process, release and stability sampling should be representative of the whole length and widthof the laminates. The formal stability programme should include any clinical batch (e.g., those used in phase 3, PK, BE, adhesion, or irritation and sensitization tests). 19,20 All batches utilised in clinical and BE trials, including placebo batches, must have executed batchrecords and certificates of analysis. All inactive chemicals, 291 components, and representative printing should be included in placebo batches.

**3. Product Characterization Studies**

Because of the uniqueness of the TDS dosage form, specialized developmental studies andevaluations are recommended to demonstrate full product understanding in both new and abbreviated new drug applications. Several such studies/evaluations are discussed below,

**a. Skin Permeability**

Skin permeability is a function of permeant thermodynamic activity and degree of saturationof the drug substance in the TDS. The solubility and degree of saturation of the drug substance in the TDS should be evaluated, and their impact on the performance of the TDS understood.

**b. Crystallization**

Generally, crystallization of the drug substance in the TDS product should be avoided. If crystallization occurs, studies should be conducted to assess its impact on the in vivo performance and adhesion of TDS.

**c. Thermodynamic Stability of Drug Substance**

To confirm thermodynamic stability of the drug substance, the risk of precipitation or salt formation during manufacturing and storage should be evaluated. If there is an equilibrium between different salt forms, the kinetics to reach this equilibrium should be thoroughly characterized. The impact of this equilibrium on TDS performance should be evaluated withrelevant in vitro drug release, permeation, and/or clinical data

**d. Strength**

The strength of a transdermal system should be expressed as a rate (e.g., XX mg/day), whereas the strength of a topical system should be expressed as a percent total drug load. Fortransdermal systems, the strength can be derived from and supported by either PK data or byresidual drug analysis performed on used transdermal systems. The first approach involves the derivation of a clearance (Cl) value from absolute bioavailability of the drug and multiplying that by the concentration (Css) at the steady state. The second approach involvesthe measurement of the amount of drug left in the transdermal systems at the end of the wearperiod and dividing "consumed amount" by the wear period. Although the strength of a topical system is expressed as percent total drug load, a residual drug analysis should still be conducted.

**e. Residual Drug**

Consistent with FDA guidance for industry Residual Drug in Transdermal and Related DrugDelivery Systems (August 2011), scientific justification sufficient to support the amount of residual drug in a TDS should be included in the pharmaceutical development section of theapplication. To provide a robust analysis of the residual drug, we recommend the following: Contains Nonbinding Recommendations Draft — Not for Implementation 12

1. Data should be based on analysis of the used TDS and not on a theoretical calculation.

2. The amount of drug left on the skin surface should be assessed. Any drug that may have been transferred to packaging or other components of the TDS during storage or use shouldbe accounted for in an attempt to perform a mass balance.

3. Tape or overlays should not be used in studies where the TDS is used to calculate residual drug.

4. TDS adhesion assessments should be conducted over the entire period of wear to determine whether the TDS diffusional surface area remains in full contact with the skinduring the entire period of the study.

5. A control study should be performed to provide an estimate of drug load, rather than simply using the expressed label claim. This study should include analysis of a minimum ofthree unused products from the same lot of product used in the study.

6. Sample storage conditions before and after application of the TDS on the skin should be validated. Photostability and thermal stability of the active ingredient(s) in the TDS shouldalso be considered when selecting the appropriate storage conditions.

7. Appropriately sensitive and valid analytical methods should be used to assay the residual drug content for the purpose of calculating drug depletion and delivery. When estimating theamount of residual drug in the TDS, a drug extraction method with a target extraction efficiency close to 100 percent should be utilized to minimize error.

**f. In Vitro Permeation Testing**

In vitro permeation testing (IVPT) with the use of excised human skin may be utilized tocharacterize the rate and extent of transdermal or topical drug delivery, and the study protocols and results should be described in the application.

The following factors should be considered 386 during IVPT model development:

- Selection of the diffusion apparatus and the operating conditions like stirring rate or flowrate, as well as temperature control to maintain the under-normal-conditions skin surface temperature (32℃ ±1℃)
- Source of the skin, skin storage conditions, choice of skin type (i.e., age range, sex, race,and consistent anatomical region) and the skin preparation technique (e.g., full-thickness, dermatomed, isolated epidermis)

The IVPT methodology should define the nominal skin thickness and its range, the skin barrier integrity test details, and any product occlusion during the IVPT. Visual observations alone are insufficient to define the skin's barrier integrity. Barrier integrity studies based on tritiated water penetration, trans-epidermal water loss (TEWL), or electrical impedance/conductance measured across the skin are all acceptable. The skin barrier integritytest parameters and acceptance criteria should be supported using relevant research references or other information.

The IVPT protocol should also contain information on the receptor solution, system equilibration, skin mounting and TDS application processes, and any precautions to secure the TDS on the skin surface to avoid lifting. We propose that an antibacterial agent (e.g., 0.1percent sodium azide or 0.01 percent gentamicin sulphate) be added in the receptor solution.

The IVPT research report should include the following information: dosage duration, sampling duration, sampling time points, sample concentration, antimicrobial component concentration, and empirical stability (at relevant temperatures) and solubility of the active ingredient in the receptor solution. The number of people whose skin was examined (i.e., skindonors) and the number of duplicate skin sections per donor per treatment group should also be included in the study report.

In an IVPT trial, all treatment groups should be dosed on skin samples from the same set of donors, with the same number of duplicates per donor per treatment group. These treatment groups should also employ skin samples from the same anatomical site from all donors, unless altering these parameters is required for the study's design and TDS assessment. The equilibrated skin surface temperature prior to dosage application, as well as the ambient temperature and relative humidity in the laboratory, should be included in the research report,as should the level of qualification of the sample analytical procedures (e.g., HPLC)

**g. Extractable and Leachable Testing**

All TDS should be evaluated for potential compounds that could be transferred from theproduct to the patient. This evaluation should include assessments of extractable and leachable, consistent with USP.

As defined in United States Pharmacopeia (USP)21 General Chapter Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems, “extractable areorganic and inorganic chemical entities that are released from a pharmaceutical packaging/delivery system, packaging component, or packaging material of construction andinto an extraction solvent under laboratory conditions.” The extraction conditions should “accelerate or exaggerate the normal conditions of storage and use for a packaged dosage form.” As defined in USP General Chapter Assessment of Drug Product Leachable Associated with Pharmaceutical Packaging/Delivery Systems, “leachable are foreign organic and inorganic entities that are present in a packaged drug product because they have leached intothe packaged drug product from a packaging/delivery system, packaging component, or packaging material of construction under normal conditions of storage and

use or during accelerated drug product stability studies.

Extractable studies are used to inform the leachable study design. The leachable data should be correlated, if possible, with the extractable profile(s) determined under the various controlextraction study conditions. Both extractable and leachable studies should have adequate sensitivity to detect compounds potentially released at a level associated with patient exposure when a product is used at the maximum daily dose (e.g., 1.5 mcg/day for standard

mutagenic compounds in a chronic-use drug product), unless otherwise justified. For someproducts, the maximum daily dose may require applying more than one TDS.

To aid in the extractable and leachable analyses described below, applicants should contactraw material suppliers to identify potential extractable of toxicological concern, such as residual monomers from backing materials:

**i. Extractable Studies**

Extractable studies should be carried out early in the pharmaceutical development phase to identify possible leachable from components of the intended commercial TDS. These tests should be carried out on components such as the backing membrane, the release liner, the rateregulating or other internal membranes, the ink, and the pouching. To maximize the amounts of extractable and detect as many potential leachable as feasible, the testing components should be extracted in a number of solvents with a range of polarity under strong laboratory extraction conditions. The solvent of the proposed commercial adhesive(s) platform or the known residual solvents for the completed 484 TDS should be one of the extraction solvents employed in the extractable experiments. The solvents used should be reasonable

**ii. Leachable Studies**

The circumstances of the leachable experiments should be as near to the "worst-case" clinicalsituations of the skin as feasible (e.g., sweating during rigorous exercise). The solvent/solution selection (such as salt concentrations), temperature, agitation level, length ofsolvent exposure, and other parameters used in the experiments should be justified. During the investigation, the release liner should be withdrawn from the system to properly expose the adhesive layer to the physiologically relevant solvent. Applicants should do a multi- timepoint leachable study (e.g., 0, 6, 12, 24 months) to give a thorough leachable profile and detect any trends in leachable, since these data may affect the product's shelf life. At the time of application submission, data should be submitted from a leachable study performed on samples from multiple batches stored at a minimum of 6 months under accelerated and long term conditions. We recommend conducting leachable studies on the same three distinctlaminates of TDS placed on stability testing.

**h. Assessing the Effects of Heat**

We recommend that heat impact studies be undertaken as part of a clinical trial utilizing theproposed commercial product for a TDS product to be presented in an NDA. Critical elements such as suitable raised test temperature(s), heat exposure initiation time(s), duration(s), and cycles (if any), as well as heat exposure techniques (e.g., heating lamp, heating pad, etc.) should be determined when developing heat impact research. In order to submit a TDS product in an ANDA, the applicant must determine if the test TDS, when utilized

under increased temperature settings, enhances drug delivery relative to the reference (R) TDS. The ANDA applicant should provide the results of an IVPT study comparing the drug delivery characteristics for the test TDS and the R TDS at normal and elevated temperatures using skin from multiple individuals (donors), with multiple replicate diffusion cells evaluated per donor, per treatment (test versus R), and per temperature condition. An IVPT research with a significant number of donors and duplicates per donor per treatment per temperature condition is advised to acquire relevant results. A trial with fewer than four donors and 523 four replicates per donor per treatment per temperature.

We recommend a parallel evaluation and comparison of the test and R TDS under thefollowing baseline and elevated temperature conditions:

1. BASELINE: Both the test and R products should be maintained at a TDS/skin surfacetemperature of 32 ±1°C for the entire study duration.
2. ELEVATED TEMPERATURE: Both the test and R products should be maintained at a TDS/skin surface temperature of 32 ±1°C until a specified time, approximately when the peak flux is observed, and then maintained at a TDS/skin surface temperature of 42 ±2°C fora period thereafter, which may be the remainder of the study duration.

It may be adequate to perform an IVPT study for a 48 or 72-hour duration, if that duration issufficient to reach the peak drug delivery rate under baseline conditions. Alternatively, an applicant may justify evaluating other conditions or scenarios of exposure to elevated temperatures that represent the worst-case scenario for a given TDS product or indicated patient population.

i. **Microscopic Matrix Evaluation**

Adhesive matrices frequently do not form real solutions due to the intricacies of many TDS formulations, but rather manifest as dispersions. Rearrangements of the dispersed-like systeminside the matrix over time may result in a lack of adhesion or alterations in drug delivery andrelease. As a result, it is critical to understand the TDS formulation, how the therapeutic component and excipients are spread within the adhesive matrix, and how the matrix tends to vary over time from product release to expiry. As a result, using high-powered microscopy, elemental mapping, or other relevant methods, examine surface and cross-sectional changes in the TDS matrix over the shelf life of the developing batches.

4. **Proposed Manufacturing Changes**

Scale-up plans and other process modifications may be included in an initial NDA or ANDA,but the amount of extra material required to support these changes will typically be proportional to the risk that the change may have a detrimental impact on product quality.

Because TDS is sensitive to slight changes in formulation and manufacturing process, alterations to TDS following crucial clinical trials should be avoided wherever feasible.

Moderate-risk adjustments may need further developmental studies and stability data on commercial size batches to demonstrate that they will not have an unfavorable effect on product quality. Scaling-up of hot-melt mixes by a factor of 10, scaling-up of screw-based mixing processes, and adjustments to coating/drying/laminating equipment of the same design and working principle are examples of such alterations. Changes that offer a significant risk to quality may necessitate more in vivo research. Changing

the productionprocess to include equipment of a different design and operating principle is one example.

## B. Manufacture

As described in ICH M4Q, section 3.2.P.3 of the application should contain information about where and how the TDS product will be manufactured. The batch formula and a description of the manufacturing process and process controls should be provided. A detailedschematic diagram of the proposed production process, including descriptions of the equipment, operating conditions, and process controls, should also be provided. During process development, the applicant should identify process variables that have a potential to impact TDS product CQAs. These process development studies inform commercial process qualification and continued process verification later in the product lifecycle. Typical TDS manufacturing steps/unit operations are listed below (a non-exhaustive list).

For processes that incorporate these steps, the applicant should describe how each operationand associated controls were developed, addressing the considerations below, specifically, the CQAs that may be impacted by the operation, and the relevant process parameters and material attributes that may impact the output of each operation.

- Mixing procedures provide bulk mixes for the coating stage. CQAs such as assay, stability of drug component and/or excipients, content homogeneity, microscopic appearance, and physical characteristics of the adhesive can all be affected by mixing.The control strategy should address the impact of equipment design, order of material addition, and process parameters (such as mixing speeds, mixing times, temperatures,redispersion or recirculation conditions, and deaeration conditions) on CQAs and, if necessary, be justified using development studies. Drug ingredient particle size, polymorphic shape, raw material rheological properties, and percent solids for materials delivered in solvent-based mixes are all CMAs that might influence mixing.
- Coating, drying, and lamination are all terms used to describe the application of a mixture to a substrate. Coating can have an influence on CQAs such as content consistency and microscopic appearance depending on the equipment employed. Despite the fact that CPPs are equipment dependent, enterprises must demonstrate that the control approach (e.g., process parameters to be regulated) is enough to assurecontent homogeneity and microscopic appearance throughout the duration of the coating operation. CMAs that can affect coating include bulk mixture rheology and within-roll homogeneity of the substrate to be coated.

Drying involves the removal of solvent from the mixture following the coating process. Thisprocess step can impact CQAs such as assay, permeation enhancer content, antioxidant content, water content (for hydrogels), content uniformity, microscopic appearance, drug release, product stability, residual solvents, residual adhesive impurities, and physical properties of the adhesive matrix. Therefore, CPPs for drying that may need to be consideredduring process development include line 23 See 21 CFR part 314.50(d)(1)(ii)(c).

Contains Nonbinding Recommendations Draft — Not for Implementation speed, the pump orscrew speed, zone temperatures, air flow rates, temperature of the drying air, and humidity ofthe drying air. Process development should also consider the CMAs that can impact drying such as solvent and adhesive impurity content in the bulk mixture. Applicants should also provide data to justify any drug substance overage or excipient excess that may be needed to compensate for any evaporation during drying.

Lamination involves the combining of multiple layers of a given transdermal system design into a single common laminate. Applicants should provide development data for corona treatments if such a process is used to bond the adhesive to a backing film or rate-controllingmembrane.

1. Slitting and Printing: Typically, the bulk product is split lengthwise into thinner laminate rolls for subsequent processing. Slitting and printing are normally low-risk stages; however, if certain characteristics of the printing processes, such as excessive penetration depth or heatinput, might have an undesirable effect on product quality, then the printing processes shouldbe described and managed.
2. Converting and pouching often require cutting a continuous laminate into separate units and sealing the unit in a heat-sealed pouch. CQAs impacted by these procedures include product usability (e.g., the ability to remove a release liner) and pouch integrity. Heat sealingtemperatures and dwell durations are common CPPs for these procedures.
3. Curing: Some TDS require further processing processes after drying or pouching to complete the curing reaction. CPPs for this stage include curing time and curing conditions. Ifcuring might affect test findings, it should be finished before batch release testing.
4. Hold times: Hold times for in-process materials retained between unit operations must beestablished and justified (21 CFR part 211.111). Applicants should choose which CQAs to monitor during hold time studies using a risk-based strategy.
5. Other considerations: Non-reactive, non-additive, and non-absorptive tubing and other product-contact equipment must be certified (21 CFR part 211.65(a)). The tubing and certain

product-contacting equipment should be chosen based on risk, i.e., the duration of contact, process temperature, solvent system, material considerations, removal of leachable duringmanufacture, and clinical usage concerns.

## C. Control of TDS Product

Section 3.2.P.5 of the application should contain the following information on control of the700 TDS product:

- Specification
- Analytical procedures
- Validation of analytical procedures
- Characterization of impurities
- Batch analyses
- Justification for the proposed specification Typical CQAs included in TDS specification:
- Description
- Identification
- Assay
- Impurities and degradation products

- Uniformity of dosage units
- Permeation enhancer content, when applicable
- Adhesion
- Release liner peel
- Tack
- Shear
- Cold flow
- In vitro drug release
- Drug substance crystal presence
- Pouch integrity
- Microbial limits, when applicable
- Moisture content, when applicable
- Residual solvents

Some of the methods and criteria associated with CQAs typical for TDS are described below.

## a. Adhesive Impurities

Adhesives may contain leftover monomers, initiator by products, aldehydes, and other contaminants. The safety of these chemicals should be evaluated because some of them areneurotoxic (e.g., tetramethyl succino nitrile) or mutagenic (e.g., crotonoaldehyde).

Manufacturers are recommended to contact raw material suppliers to discuss the selected adhesive raw material and any potential impurities, since certain contaminants may not be indicated on the supplier's certificates of analysis. In the application, applicants should address the probable contaminants coming from the raw material. A toxicologically relevantimpurity control approach should be devised and justified. Testing at the raw material stage, verifying that the production process is capable of reliably eliminating the contaminants of concern, and testing of the finished product are all examples of control strategies.

## b. Uniformity of Dosage Units

TDS specifications should include a test and acceptance criterion for content uniformity for the dosage units. If the finished TDS is designed to be cut by the user, uniformity should alsobe demonstrated among pieces cut from a single unit

## c. Permeation Enhancer Content

Products that utilize permeation enhancers to establish or maintain drug delivery should include a test and acceptance criterion for permeation enhancers at release and throughoutstability. An acceptance criterion that is wider than the typical range for a particular permeation enhancer may require in vivo justification in the absence of an in vitro in vivocorrelation

### d. Adhesion Testing (Peel Adhesion, Release Liner Peel, Tack, and Shear Tests)

In vitro adhesion testing does not correspond to in vivo adhesion with currently available methods, however it can be beneficial for quality control (QC). Peel adhesion, release linerremoval, tack, and shear should all be tested in vitro (dynamic or static).

Each test has several procedures and varied experimental settings.

The peel adhesion test determines the force necessary to remove (peel away) a TDS from astandard test panel (e.g., polished stainless steel). The test factors that determine peel adhesion measurement include dwell duration, substrate (e.g., stainless steel, high density polyethylene (HDPE)), peel angle, and peel speed. A release liner peel test determines the amount of force necessary to separate a TDS.

## e. Cold Flow

Cold flow is the creeping or leaking of the adhesive matrix beyond the backing membrane's perimeter or through the release liner slit. The TDS, release liner, pouch, or disposable films may all have cold flow (sometimes termed slip sheets or protective films, such as a film over the backing and a film over the release liner). A quantitative approach of evaluating cold flowcan offer a relevant assessment, but it may not represent the difficulties in extracting the TDSfrom the pouch or the protective films from the TDS. A combination of product-specific quantitative and qualitative approaches will most likely provide the most accurate cold flow TDS measurement. The test procedures used should be discriminatory and scientifically supported.

## f. In vitro Drug Release

USP General Chapter describes the apparatuses to use for in vitro release testing and the acceptance criteria for each apparatus; however, method development and validation is not addressed. General recommendations for in vitro release testing of TDS are described belowalong with considerations for method design and validation.

In vitro drug release testing of TDS products is typically performed using specific, qualified apparatus such as: Paddle over Disk (Apparatus 5), Cylinder (Apparatus 6), or ReciprocatingHolder (Apparatus 7).

The NDA or ANDA submission for the TDS product should include a method developmentand validation report with complete information/data supporting the proposed drug release method and acceptance criteria.

The acceptance criteria for the in vitro drug release test should be based on the proposed TDSproduct batch release data, including data from bio-batches (e.g., BE, PK, Clinical), registration/exhibit batches, and commercial batches (if available). To set the acceptance criteria for the in vitro drug release test, a complete drug release profile should be establishedby collecting data until there is no increase in drug release over three consecutive time points (sampling every 2 hours).

The drug release profile of TDS products typically encompasses initial, middle, and terminalphases; thus, for setting the acceptance criteria, there should be at least one sampling time point covering each phase. The drug release data should be reported as the cumulative percent of drug being released with time.

The acceptance criteria range for each specific timepoint should be based on the mean percentage value of drug released ± 10 percent using the drug release data generated at these times. The percentage should be determined based on the TDS product's label claim. If less than 100 percent drug is released, but no drug increase is observed over three consecutive sampling timepoints (i.e., incomplete drug release), the amount of drug reached at the plateaushould be considered 100 percent for the purposes of estimating the percent of drug release over time.

## g. Crystal Presence

The presence of crystals in the TDS or crystallization of the medication over time might havea detrimental influence on product performance. As a result, it is critical to develop a test andacceptance criteria to validate the absence of crystals to be employed during release and stability. Rather of a simple visual count, microscopic and photometric approaches are utilized. While it is true that certain goods are meant to be suspensions, this does not eliminate the necessity for a crystal specification. Suspension products should still incorporate testing and approval criteria to prevent crystal propagation, which might affect medication delivery or adhesion qualities.

## h. Pouch Integrity

The bag for a TDS is crucial to the product's stability and integrity. Unless an alternatetechnique that ensures the completed product specification is available, pouch integritytesting should be performed as part of the finished product release.

## D. Additional Stability Studies

TDS applicants and manufacturers should conduct stability studies under challenge conditions such as temperature excursions, freeze/thaw, and/or crystal seeding, in addition tothe standard battery of formal stability and photostability studies for drug substance and drugproduct discussed in ICH Q1A and ICH Q1B. These further research will target specific product quality challenges such as crystal formation and growth. Furthermore, depending onthe opacity of the backing membrane, the duration of use, and the predicted 901 exposure to light when in use, in-use photostability testing may be acceptable for specific TDS formulations.

## 1. New applications:

The information needs covered below apply to new generic or condensed applications as wellas new active substance transdermal patch systemic delivery applications. Section 5 Standards to Support a Generic or Abbreviated Application provides additional criteria for generic or abridged applications in place of full clinical data.

**1.1 Description and composition of the drug product**:

The description must be thorough enough to adequately characterize the drug product (in all strengths) and to provide information to the SmPC's relevant quality departments, as well as,if necessary, the packaging leaflet and labelling.

The product description should include the following:

- Strength is defined as the mean mass delivered in vivo every 24 hours as a doseadministered over a unit of time.
- The strength or rate of in vivo release per patch area (i.e., the mass supplied in vivo perunit area per unit time);
- The amount and location of the drug's active ingredient;
- Active ingredient utilization (per patient administration, the percentage of the total activesubstance absorbed);
- Patch area activity (patch area for active substance use);
- Residual (the amount of active ingredient in a drug product that is still present afteradministration);
- Useful instructions, including how to apply any overlays; and
- Patch period of use.

Unambiguous tabular formats, any necessary schematics (preferably supported byphotographs) should be provided to describe the following:

- Patch type, with respect to the control of drug release (e.g., reservoir, drug in adhesive);
- The form and function of each layer of the laminated product;
- The composition of each layer, including the function and the grade of the excipient (thegrade is normally considered to be a critical quality attribute for transdermal delivery). Backing layers and release liners should also be described;
- Overlay description (if applicable);
- Patch size, area and thickness (area weight may be considered if justified); and
- Appearance, including shape, color and markings.

It is also important to describe characteristics of drug product design that relate to patientadministration and use over the course of use.

Transdermal patch design should avoid cutting by patients or health care professionals – asmaller transdermal patch should be developed instead.

However, in exceptional cases for good patient safety and efficacy reasons, cutting might benecessary. In such cases this should be described and supportive data should be given in

3.2.P.2 as well as in the clinical dossier.

If necessary, a brand name or the name and address of the producer should be used to supportthe name of excipients that are not listed in a pharmacopoeia.

The primary packaging and, if necessary, secondary packaging or other materials orcomponents required for reasons of stability, should be described.

Quality tests cannot directly or indirectly (using surrogate indicators) determine several aspects of the description of the drug product, such as product strength, active substance utilization, residue, and acceptability of administration and usage. Only relevant, valid clinical investigations can determine and/or evaluate these quality components. Cross references to other dossier sections that detail their determination and/or assessment, as wellas proof of the reliability of the clinical procedures, should therefore be included in the description.

### 1.2 Pharmaceutical development

The pharmaceutical development component of the dossier should form a sound basis of thesuitability of the transdermal patch for its intended use, provide a clear narrative of product development and include all relevant data.

#### 1.2.1. Therapeutic objectives and principle of the delivery system

In terms of patient benefit and risk, a synopsis of the treatment goals and the justification forselecting the transdermal route for the active ingredient should be included.

Therapeutic use, local and systemic adverse effects related to alternative routes, pharmacodynamics, and pharmacokinetic features of the active agent (such as t1/2,therapeutic index, and first pass effect) should all be taken into account.

The proportionality of various strengths, local tolerance, the method of administration (including occlusion, if applicable), administration site, and posology should all be examined.

Cross references to pertinent clinical parts of the dossier should be provided when applicable.

For example, the identification and description of the type of transdermal patch (e.g., reservoir, drug in adhesive) and how drug release over the intended time of application isachieved should be included in the discussion of how the design and function of the transdermal patch achieve the therapeutic objectives.

#### 1.2.2. Active substance

Active ingredient Physical, chemical, and biological characteristics that affect a drug's ability to be manufactured, its stability, and rate and extent of transdermal administration should be discovered and explored. These characteristics include molecular weight, partition coefficient, melting point (and boiling point, if applicable), pKa, solubility, and pH effects. Ifthe active ingredient is present in the drug product in the solid form, these characteristics alsoinclude physical characteristics like particle size and polymorphism. The desired physical state of the drug substance, such as a solute, suspension, and the level ofsaturation or super saturation, are crucial quality attributes that should be justified in terms of the product's effectiveness and safety, with supporting data showing how the desired state is achieved during manufacturing and how stable it is during storage.

The risks of precipitation / particle growth / change in crystal habit, or other active substancecharacteristics likely to affect the thermodynamic activity, arising from changes in temperature and on storage should be assessed and appropriate tests included in the stability studies.

These properties could be inter-related and might need to be considered in combination.

### 1.2.3. Excipients

In relation to their separate roles, the selection of excipients (including the adhesives, backinglayer and release liners, and rate control membrane) as well as their concentration and features should be reviewed.

Detailed information on those materials which might have an influence on the adhesive properties and active substance transdermal permeation and bioavailability (e.g. solubiliser, penetration enhancer or retarder) should be provided, including their ability to provide theirintended functionality and to perform throughout the intended drug product shelf life (see also the Note for Guidance "Excipients in the Dossier for Application for Marketing Authorization of a Medicinal Product" CHMP/QWP/396951/06 Annex III)

The suitability and performance of a rate-controlling membrane should be thoroughlyexamined for patches that use one.

It is important to discuss the pertinent properties of the layers (backing layer, release liner, rate-controlling membranes, and adhesive liner), including appearance, flexibility, tensile strength, porosity, occlusion, chemical inertness, and porosity. As necessary, this informationcan be utilized to support the drug product specification as well as to defend the selection, specification, and safety (3.2.P.4.4 and 3.2.P4.6) of the excipients (3.2.P.5.6).

Excipient mix composition and pertinent details, such as viscoelastic qualities if necessary, should be included. Examples of these excipient mix details include sticky solutions or suspensions. It is important to recognize and explain any processing aids, such as temporarylamination layers and solvents used during manufacturing but afterwards removed.

### 1.2.4. Formulation development

Using appropriate tests to characterize and control the critical quality attributes, such as adhesion properties, factors affecting ease of administration and duration of use, and productperformance, the development of the drug product should be described in relation to the defined quality target product profile (dissolution, in vitro drug release, in vitro skin permeation).

Satisfactory evidence of the suitability of the methods employed should be provided (see alsoSection 4.2.6 In Vitro and in vivo Drug Product Performance and Annex 1 In vitro Permeation Studies)

Transdermal patches should show satisfactory evidence of compliance with Ph Eur criteria.

It is important to clearly examine the connection between the Finished Product Specification,the Critical Quality Attributes, and the Product Quality Profile. Physicochemical and solubility qualities of the active ingredient in the formulation, stability, drug release, and the pace and degree of drug penetration should all be considered during product development.

The manufacturing process will be scaled up once the formulation composition is determined,and the crucial process variables will be identified and managed.

It is reasonable to anticipate that changes will be made in order to achieve and optimise full- scale manufacturing throughout this time. These modifications could involve modifications tothe composition, production methods, tools, or manufacturing facility.

These modifications may occasionally have an impact on the therapeutic product's in vitro release/dissolution, in vitro skin penetration, and in vitro adhesion qualities; as a result, theyshould be evaluated.

It is necessary to provide a thorough description of both the batches utilised in the pharmacokinetic investigations and the clinical trial formulation. Any formulation and manufacturing variations between clinical batches and the final product should be explained.Results from comparable in vitro research (such as drug release/dissolution, skin permeability, adhesion), as well as comparative in vivo studies (such as bioequivalence), ought to be presented.

Understanding the crucial formulation and production factors that affect the drug product'sadhesive qualities may assist minimal adjustments in the adhesive composition.

In terms of quality in relation to efficacy:

A strong justification, in vitro quality testing, and clinical evidence should be used to supportthe active substance quantity, formulation, patch size, and thickness. The product development process should also be well explained.

In terms of quality in relation to safety:

Those quality elements that may influence the safety of the drug product such as material specifications, qualification, identification and control of residual solvents and impurities should be discussed. The risks of dose dumping, leakage from reservoir, residuals and product residues should be discussed. Cross reference to relevant non-clinical or clinical datashould be given.

In terms of quality with respect to the administration and use:

Both in vitro and in vivo testing should be done to fully evaluate and characterize themedication product's sticky qualities.

The balance between adhesion and cohesion should be taken into account while minimizing cold flow (the formation of a "dark ring" around the transdermal patch while it is being used),ensuring enough elasticity, and preventing detachment, edge lifting, or skin damage while using it.

The Ph. Eur. adhesion specifications must be followed. The protective liner cannot be removed without removing the preparation (matrix or reservoir), and it cannot be removedwithout removing the adhesive from the patch.

The transdermal patch should stick securely to the skin with gentle hand or finger pressure and be easy to peel off without significantly damaging the skin or separating the preparationfrom the outer layer.

The design elements of the drug product to ensure satisfactory practical administration shouldbe discussed.

### 1.2.5. Stability programme development

The proposed stability programme (3.2.P.8) should take into account the product understanding gained during pharmaceutical development. This should include performancetests with respect to (a) dissolution, (b) drug release using a synthetic membrane and (c) skinpermeation testing, as appropriate, and adhesion.

A successful drug product stability procedure should be created after a thorough discussion ofthe risk factors for product stability.

The stability programme should make sure that the drug product is subjected to suitable stressful and real-time storage circumstances (including temperature cycling), indicative ofthe authorized marketing of the product.

The requirements for special storage warnings e.g., do not refrigerate, should be addressed.

With respect to physical stability, factors should include formulation changes arising from active substance and / or excipient evaporation or migration, active substance crystallization or other change in its thermodynamic activity, changes in the state of excipients. Changes inadhesion properties under different storage conditions should be assessed.

To support (any) proposed holding times and storage conditions, the stability of intermediate products, including laminated rolls should also be subject to a stability programme.

### 1.2.6. In vitro and in vivo drug product performance

#### 1.2.6.1. In vitro drug release / dissolution:

A transdermal patch's ability to release an active ingredient is assessed using an in vitro release test. The final product release and shelf life criteria must include this crucial qualityattribute even though the test may not accurately simulate in-vivo performance.

The dissolving test or the release test employing a suitable, non-rate-limiting membrane should be performed in accordance with the procedures outlined in the Ph. Eur. Monograph for Transdermal Patches. If necessary, alternative techniques with greater discriminatorypotency than compendial techniques may be used.

The transdermal patch's functionality should not be harmed or otherwise altered by the test or sample preparation. It should be discussed if there are any unique needs for sample preparation. If it can be demonstrated that sample preparation has no effect on drug release ordissolution, it might be possible to test only a certain patch sample region that is appropriate to all strengths. The suitability of testing specimens may be determined from dose proportionality studies for samples of various sizes if the size of the patch is too large to fit into a normal dissolve testing device or if sink conditions cannot be attained using whole patches.

The drug product's active ingredients in vitro drug release / dissolution profile should be characterized and established from clinical batches for which sufficient efficacy has been shown. These should be utilized to support the in vitro drug release / dissolution limitationsspecified in the drug product specification (3.2.P.5.6), as they guarantee that subsequent production batches will be of a quality comparable to the pivotal clinical batches.

Satisfactory evidence of discrimination should be provided, with respect to:

- Critical manufacturing variables;
- Excipient and active substance critical quality attributes; and
- The stability indicating power of the method.

A summary of the development of the dissolution test should be provided, where the transdermal patch is tested under various conditions (media, pH, apparatus, agitation, etc.).Testing conditions providing the most suitable discrimination should be chosen. In case ofmedia with a low buffering capacity, the pH should be controlled during the dissolution test to avoid influence of thedissolved active ingredient and/or excipients on the dissolution conditions during the testperiod.

The test period should be sufficient to achieve complete drug release, unless justified.

With more frequent sample throughout the period of maximum change, there should be enough sampling time points for the release / dissolution profile to produce relevant profiles.

At least 3 sampling time points are recommended to give a sharper and more differentiatedprofile.

Early time points to rule out dose dumping and/or characterized a loading or initial dose (typically 20 to 30% dissolved), at least one point to ensure compliance with the shape of thedissolution profile (around 50% dissolved), and one point to make sure the majority of the active substance has been released (typically more than 85% dissolved, i.e. Q=80%).

Early sample times (between 0 and 1 hour) for the majority of matrix type patches were found to be more discriminative, or quality indicating, than later time points, when up to 50%of the active substance had already been released from the patch. If the specification ranges are specified in line with the following criteria, changes in formulation or manufacturing parameters are more likely to be identified within the first hour of in vitro dissolution testing.

The amount of active material released in mass units (mg or g) per surface area should bereported for the dissolution profiles at each time point. Reporting the amount of active ingredient as a percentage of the total is also necessary.

The value to be provided at each time point should be the amount of active material releasedper surface area, per time. In addition, the first derivative of this profile should also be supplied, to allow assessment of the change in release rate over time.

For transdermal patch products showing an in vitro zero order release (e.g., which may be seen in those patches with a rate-controlling membrane) a specification of the dissolution rateat a given time point may be more appropriate than the cumulative amount dissolved at a given time point.

The minimum number of samples per batch that should typically be used to characterize thedissolution profiles is 12. (for routine release, a minimum of 6 units would be accepted).

Data on the profile of dissolution should be presented in tabular and graphical forms, alongwith a measure of variability between units, such as a 95% confidence interval, range, or other justifiable statistical technique.

The dissolution profiles should be discussed taking into account the type of transdermalpatch.

Dissolution limits should to be fully justified and based on data. They ought to reflect production capacity

and correspond to clinical batches where good efficacy has been shown.

Normally, the permitted range in mean release at any given time point should not exceed a total numerical difference of ±10% of the labelled content of active substance (i.e. a total variability of 20%: a requirement of 50±10% thus means an acceptable range from 40-60%), unless a wider range is supported by a bioequivalence study.

Only when well justified on quality grounds and substantiated by a bioequivalence study may wider limitations be authorized.

Release and shelf life limitations should usually be the same, unless there are quality-related justifications for the variances that can be supported by using clinical batches. To guarantee that the product will remain within the shelf life criteria, stricter restrictions should be placedupon release.

**1.2.6.2. In vitro skin permeation studies**

In vitro permeation tests, which reflect the thermodynamic activity of the product's active ingredient, may be regarded as a useful indicator of product quality even though they are notoften expected to correlate to in vivo release.

Currently, in-vitro skin permeation studies are not appropriate for routine batch control testing; rather, they should be utilized to guide and evaluate the development and optimization of the therapeutic product formulation. To offer corroborating stability data on product performance during storage, permeation experiments might be included to the stability study protocol, albeit with less frequency.

In vitro skin permeation should be consistent throughout the shelf life of the drug product.

Establishing the characteristic permeation profile of the drug product, using a discriminativein vitro skin permeation method, can be of value in change control during life cycle management (see Section 6 Variation Applications).

**1.2.6.3. Adhesive properties**

**1.2.6.3.1. In vitro adhesion tests**:

The transdermal patch's adhesion/cohesive characteristics should be evaluated using in vitroadhesive testing. Despite the possibility that these tests do not accurately simulate in vivo adhesion, they are crucial quality characteristics that must be mentioned in the finished product release and shelf life specification.

Peel force tests (the amount of force needed to remove the patch from the release liner), adhesive strength tests (the amount of force needed to remove the patch from a specified surface), and tack tests are a few examples of experiments that can be used to determine anadhesive's qualities (maximum force required to break a bond formed under low pressure between the adhesive layer of the patch and a stainless steel probe). Residue remaining on the release liner after peeling from the patch and skin residues,following transdermal patch removal, should also be addressed.

It is important to justify the breadth and sufficiency of the in vitro experiments utilized todescribe the adhesive qualities of the therapeutic product. If necessary, a synopsis of theirevolution should be offered to back up any justification.

The suitability and discriminatory power of the test methods employed to characterized the adhesive properties of the drug product need to be proven during product development, in particular with respect to:

- Critical manufacturing variables;
- Excipient and/or active substance critical quality attributes; and
- Stability indicating power of the method.

The drug product's in vitro adhesive properties should therefore be defined, with the specifications limits for the specified tests in accordance with the results obtained on clinical batches for which satisfactory in vivo adhesive properties under product use have been shown and used to support their justification of the drug product specification (3.2.P.5.6) (see also Section. Administration).

Release and shelf life limits should be the same, unless justified by reference to clinical batches.

**1.2.6.3.2. In vivo adhesion studies**

Studies should be conducted to determine the drug product's satisfactory in vivo adhesive performance.

Since an in vivo adhesion study is pivotal for approval, a feasibility or pilot study could be helpful in ensuring the methods can be satisfactorily undertaken, producing result from which valid conclusions can be made.

The evaluation should be done over the entire suggested time frame of using the patch. This is because reliable clinical conclusions would need acceptable adhesion performance of the clinical batches employed (see also Guideline on the Pharmacokinetic and Clinical Evaluation of Modified-Release Dosage Forms).

The clinical batches should be representative of the product to be marketed (see Section 4.2.6.5 Product Batches used in Clinical Studies).

**1.2.6.3.4. Pharmacokinetic studies**

A summary of all the bioavailability and pharmacokinetic studies should be given.

The data should include information on pharmacokinetics, e.g., AUC(0 - t), tmax, AUC0 - ∞, Cmax, and other relevant parameters.

It is important to explicitly identify the pivotal studies that were utilized to assess the strength of the drug product, dose proportionality between strengths (if necessary), and the amount of remaining active material.

Complete explanations of how dosage proportionality, drug residual, and drug product strength are determined should be given and linked to the clinical dossier's data.

The clinical batches should be representative of the product to be marketed (see Section 4.2.6.5 Product Batches used in Clinical Studies).

**1.2.6.3.5. Product batches used in clinical studies**

To prove that all clinical batches are indicative of the product to be commercialized, data should be submitted for each one (including sites, scales and dates of manufacture and certificates of analysis).

Both the scale of manufacturing the liquid coating mass containing the active ingredient and the scale of manufacturing the finished transdermal patches should be taken into consideration in order to be representative.

For example, full scale manufacturing for the production of laminate rolls and for roll conversion to

transdermal patches, or at least 10% of full production, should be used forstudies. These batches should be representative of the product that will be marketed andmanufactured using industrial scale equipment and conditions.

Smaller scale batches may be used for bioavailability studies if they were generated in a manner that was indicative of the full scale manufacturing process and were supported byother clinical batches that were at least 10% scale.

### 1.2.7. Manufacturing process development

The steps in the process should be identified and their purpose described.

The manufacturing process should be subjected to a risk analysis, with the essential process parameters selected based on the degree to which their variation could affect the quality of the drug product.

The selection and optimization of the manufacturing process described in 3.2.P.3.3, inparticular its critical aspects, should be explained.

The following non exhaustive list should be discussed:

- The preparation and homogeneity of the bulk drug containing and if applicable the bulk non-drug containing adhesive masses;
- The coating process, including those parameters that control the layer thickness;
- Drying, curing and where applicable the removal of residual solvents, including water foraqueous based blends;
- Laminations steps;
- The storage and handling of intermediate rolls;
- Roll conversion to transdermal patches; and
- Primary packing.

The proven acceptable ranges of the process parameters should be described and justified.

Unless supported by data demonstrating that there is no influence on the product performanceand critical quality attributes, differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in 3.2.P.3.3 should be avoided (seealso Sections 4.3 and 4.2.6.4).

The suitability of the packaging for intermediates, bulk storage, and transportation (shipping)should also be discussed.

### 1.2.8. Container closure system

Discussing and defending the utility of the container closure system (specified in 3.2.P.7) isnecessary. This should cover the choice of materials, safeguards against oxygen, light, and moisture, as well as the compatibility and safety of the drug product.

The primary package should normally contain only a single transdermal patch.

The backing layer and release liner should not be considered a part of the container closuresystem.

The stability study protocol should include the necessary tests to guarantee that the appropriateness of the container closure system is properly evaluated throughout the shelf-life.

For certain classes of drugs presenting a serious risk of harm to children, e.g., controlled drugs, it will be necessary to provide evidence of container closure child resistance according

to EN 14375:2003/AC:2006 (Child-resistant non-recolorable packaging for pharmaceutical products - Requirements and testing).

**1.2.9. Administration**

The SmPC, package leaflet and labelling should fully address the correct administration of the transdermal patch and include any necessary warnings for the safe use of the drug product. Consideration should be given to the safety of medical personnel and patients afterthe use of the product, especially for controlled drugs (e.g., opioids).

The Development Pharmaceutics package should include the data to support this informationor else include cross reference to other parts of the dossier, including the efficacy, pharmacokinetic and in vivo adhesion studies.

The suitability of the transdermal patch in use should be fully discussed. The followingshould be considered:

- The identification, markings, appearance and visibility of the transdermal patch; Accidental dosing due to lack of visibility should be addressed.
- Site of administration, and change in site per dose;
- The necessity to avoid damaged skin;
- The requirements for skin pre-treatment;
- The administration and securing the transdermal patch, including if applicable the use ofan overlay
- Effect of exposure to environmental extremes of heat and cold;
- Effect of normal human behavior such as washing, showers, sleeping, use of sun screens and moisturizers;
- Action to take in the event of adhesion failure, patch displacement or detachment, coldflow;
- Accidental transfer of patches to the skin of a non-patch wearer (particularly a child);
- Any necessary restrictions e.g., metalized backing and Magnetic Resonance Imaging, avoidance of occlusion;
- The practical suitability of any special storage conditions;
- Avoiding appeal to and inadvertent use by children;
- Avoidance of cutting of the transdermal patches; and
- Special precautions for disposal e.g., used patches should be folded so that the adhesiveside of the patch adheres to itself and they should be safely discarded and unused patches should be returned to the pharmacy.

### 1.3. Manufacture

Critical and non-critical process parameters should be included in Modules 3.2.P.3.3 and 3.2.P.3.4, and their inclusion should be justified by reference to the manufacturing processdevelopment that was done (see also Section 4.2.7 Manufacturing Process Development)

Coating solutions and intermediate materials should have hold times and storage conditionsthat are specified, justified, and supported by necessary stability and other data.

Transdermal patches are considered complex dosage forms manufactured by non-standard manufacturing processes. The scale of manufacture should be supported by manufacturing batch data at the proposed production scale. Exemption may be accepted if adequately justified by the transdermal patch manufacturer, on a case-by-case basis, as described in the guideline on process validation (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1).

In particular, the control of homogeneity and the thickness (area weight may be considered ifjustified) of the drug release and other layers, if present, together with the removal of residualsolvents should be fully validated.

### 1.4. Control of excipients, including layers and liners

Full quality information should be provided in accordance with the active substance format ifthe material(s) are brand-new or have not yet been approved for cutaneous and/or transdermalusage.

Important material quality characteristics should be regulated in their specifications, and theirlimits should be properly justified. It is important to consider the materials' safety, taking leachable, solvents, and monomers into account. If applicable, the suppliers' certificates of compliance with certain EU Directives, such as the Plastics Directive, may serve as evidence of the materials' safety.

The molecular weight and adhesion/cohesion properties of adhesive materials need to becharacterized and satisfactorily managed.

The composition for adhesive mixtures should be disclosed. Each component's qualitystandards need to be discussed and supported.

### 1.5. Drug product specifications

The specification should include appropriate performance tests for in vitro release / dissolution and adhesion (see Sections 4.2.6.1 In vitro drug release / dissolution and Section

4.2.6.3.1 Adhesive Properties in vitro tests), and it should adhere to Pharmacopoeial and pertinent ICH guideline requirements. Additionally, a complete description of the transdermal patch's appearance is required.

Unless otherwise appropriately qualified by non-clinical, clinical, or other evidence, thelimits should be consistent with representative batch and stability data.

Limits for performance testing should be supported by clinical batches that have shownsatisfactory efficacy and safety. Unless clinical data are used to support and qualify thelimitations, they should be the same at release and during the shelf life.

Crystal formation is a quality deficiency likely to adversely influence the in vivo performanceof the patch.

With the exception of suspension patches where the active substance is intentionallydispersed within the matrix, at release a transdermal patch should show no signs of crystallization.

In exceptional cases, it may not always be possible to prevent crystals from forming duringshelf life. In these circumstances, the SmPC and package leaflet should provide a sufficientdescription and explanation.

Any shelf life criteria for the presence of crystals in the drug product would need to be thoroughly supported by pertinent in vitro data on drug release, dissolution, and penetration,as well as clinical investigations, where appropriate.

Instead of a simple visual count, microscopic and photometric approaches are chosen for improved quantification.

Since residual solvents may affect adhesion and permeation enhancement, it may be necessary to apply stricter limits than those in ICH Q3C. Reference to the batch data of clinical batches for which satisfactory efficacy has been demonstrated should also be made.

With respect to other impurities i.e. degradation products of the active substance or reaction products of the active substance with an excipient and/or immediate container closure system,the specified limits should comply with ICH Q3B, Impurities in New Drug Products, and qualified by reference to the maximum daily systemic dose of the active substance (i.e., nominal release rate per day), the relative Guideline on quality of transdermal patches EMA/CHMP/QWP/608924/2014 Page 17/27 skin penetration of the impurities to that of the active substance, and clinical skin irritation safety studies.

### 1.6. Control strategy

Other relevant guidelines provide additional regulatory guidance (including ICH Q8, Q9, andQ10) on the establishment and justification of a control strategy for the drug product.

However, specific focus should be placed on transdermal patch skin adherence, in vitro skinpermeability, and in vitro drug release/dissolution.

If at all possible, pharmaceutical development should create correlations between in vitro dissolution rate, in vitro skin permeability, and in vitro adhesion tests and clinical efficacy(including in vivo skin adhesion).

It is crucial that it is validated at the commercial scale since skin adhesion and medicationrelease rate may be sensitive to scale-up effects.

## 2. Requirements to support a generic or abridged application

### 2.1. General remarks

The criteria that must be taken into consideration while creating a generic transdermal patch application are not notably different from those that were used to create the transdermal patchfor the original reference product. The data criteria for new applications should be met, and they should be supplemented by pertinent clinical and comparative quality data regarding thereference product.

## 2.2. Development pharmaceutics

The data requirements are as described under New Applications.

The studies undertaken during pharmaceutical development to determine the in vivo releaserate (mass delivered in vivo/unit area/unit time), active substance utilization and residual should be fully described.
These elements have an important influence on the medication compliance (patient friendlyto allow easy and correct use) as well as safety, including environmental safety.
In respect to the reference product, it is also important to address and discuss patch size, easeof usage, in vitro release, skin penetration, and adhesion qualities.
Since there is little to no IVIVC between quality characteristics and clinical efficacy and safety, it is necessary to establish quality testing parameters based on the quality traits displayed by the successful clinical batches. These parameters should also be representativeof the product that will be marketed.
Of special interest are those quality related issues that might directly or indirectly indicate thein vivo release characteristics of a transdermal patch e.g., in vitro drug release / dissolution, adhesion properties, amount of enhancer.
Generic patches should have preferably either the same or a higher patch area activity compared to the reference product. However, if justified that the benefit / risk has otherwiseimproved e.g., with respect to skin tolerability, adhesion properties, potential crystallization, cold flow a larger patch can be accepted. Nevertheless, patch area activity comparison to the reference product should be a crucial aim of the pharmaceutical development.
Regarding the residual, it is recognized that some formulations may require an overabundance of the active ingredient to maintain an adequate level of thermodynamic activity. The amount of residual medicine in generic or hybrid applications should not begreater than that of the reference product, unless otherwise supported by science.

## 2.3. Comparative quality and clinical data requirements

### 2.3.1. Quality

With respect to drug product quality, the following elements (see Section 4.1 Description andComposition of the Drug Product) should be compared:

- Strength, as the mean dose delivered per unit time, normally mass delivered in vivo perhour;
- The content and location of active substance in the drug product;
- In vivo release rate or strength per patch area (i.e. mass delivered in vivo/unit area/unittime);
- Active substance utilization (% of total active substance absorbed per patientadministration);
- Patch area activity (active substance utilization/patch area);
- Residual (mass of active substance remaining in the drug product after completion ofadministration);
- Instructions for use, including the use of any overlay; and
- Period of use.

With respect to in vitro performance:

Comparative drug release/dissolution, in vitro skin penetration, and adhesion/cohesive qualities should be examined, and the variations and parallels in in vitro performance between the reference product and the generic should be explained, supported by relevantdata.

The product strength for a generic or condensed application must match that of the referenceproduct. If not entirely justified, the other quality components listed above should also be thesame or similar.

### 2.3.2. Clinical

Bioequivalence with the reference product and noninferiority (lack of statistically significantdifference) with regard to in vivo skin adhesion should be shown to support a generic or condensed application. Reference is made to the (EMA/CHMP/EWP/280/96 Rev. 1 document), "Guideline on the Pharmacokinetic and Clinical Evaluation of Modified ReleaseDosage Forms."

Additionally, the generic product's non-inferiority with regard to clinical safety and localtolerance must be proven.

## 3. Variations applications

According to current variation guidance, the manufacturing process for transdermal patches isregarded as difficult in general. Exemption may be permitted if sufficiently justified by the transdermal patch manufacturer, as per the process validation guideline (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1).

A risk analysis should be carried out for any proposed change to determine how it may affectthe product's safety, quality, or effectiveness.

The following changes are considered to have a significant impact on the safety, quality orefficacy of the drug product:

- Change in the physicochemical state and / or thermodynamic activity of the activesubstance.
- Change in the qualitative and/or quantitative composition of excipients.
- Change in the manufacturing process:

- Change in a single Critical Process Parameter; and

- Changes in a number of non-critical process parameters.

- Any other change that affects the in vitro dissolution release, in vitro permeation or in vitroadhesion characteristics of the drug product.

## DISCUSSION

A transdermal patch, also termed a skin patch, is an adhesive patch that is applied to the skinand contains medication that is intended to be absorbed into the bloodstream through the skin. Transdermal patches are made to distribute the active substance(s) via the skin in a regulated manner, primarily by diffusion, with a certain pace and amount of systemic absorption.

This study gives guidance on pharmaceutical development and quality data that should be included in new drug applications (NDAs) and abbreviated new drug applications (ANDAs) to applicants and manufacturers

of transdermal and topical delivery systems (TDS).The guidelines go into detail on the FDA's current views on completed product control, manufacturing process and control, and product design and pharmaceutical development. It also covers particular difficulties like adhesion failure and the effect of applied heat on drug administration where quality is intimately related to product performance and potential safetyconcerns.

This guideline takes into consideration the standard specifications for the creation and quality of a transdermal patch for all new marketing authorization applications and variations. Additionally, detailed instructions are given regarding the data needs to support generic or condensed applications.

In this thesis discussed about overall Quality guideline consideration and pharmaceutical development, control of TDS product stability, stability of patches requirement and regulation of medical device (patches) for US and EU.

## SUMMARY AND CONCLUSION

"Any instrument, machine, contrivance, implant, in vitro reagent that's intended to treat, cure, prevent, mitigate, or diagnose disease in man" is the definition of a medical device. An adhesive patch that is placed on the skin and includes medication that is meant to be absorbedinto the bloodstream through the skin is called a transdermal patch, also known as a skin patch.

A medical device is anything created with the intention of being used in medicine. A medicaldevice must be proven to be safe and effective with a reasonable degree of assurance before governing governments allow the sale of the device in their country because using a device for medical purposes includes a significant risk of dangers. In general, as the associated risk increases, so does the amount of testing required to confirm a device's safety and effectiveness. The patient's potential benefit must increase as well if related risk does.

From this thesis give information about overall Quality guideline consideration and pharmaceutical development, control of TDS product stability, stability of patches requirement and regulation of medical device (patches) for US and EU.

As a basis I conclude that the information contained in this thesis is an important andessential part of patches for US and EU.

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