On February 2, 2024, FDA published the final rule to amend the Quality System (QS) regulation in 21 CFR part 820 (89 FR 7496, effective February 2, 2026). The revised 21 CFR part 820 is now titled the Quality Management System Regulation (QMSR). The QMSR harmonizes quality management system requirements by incorporating by reference the international standard specific for medical device quality management systems set by the International Organization for Standardization (ISO), ISO 13485:2016. The FDA has determined that the requirements in ISO 13485 are, when taken in totality, substantially similar to the requirements of the QS regulation, providing a similar level of assurance in a firm's quality management system and ability to consistently manufacture devices that are safe and effective and otherwise in compliance with the Federal Food, Drug, and Cosmetic Act (FD&C Act).

This guidance document was issued prior to the effective date of the final rule. FDA encourages manufacturers to review the current QMSR to ensure compliance with the relevant regulatory requirements.

Transdermal and Topical Delivery Systems - Product Development and Quality Considerations

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Mohamed Ghorab 240-402-8940.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

November 2019
Pharmaceutical Quality/CMC

Transdermal and Topical Delivery Systems - Product Development and Quality Considerations

Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Transdermal and Topical Delivery Systems - Product Development and Quality Considerations Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations to applicants and manufacturers of transdermal and topical delivery systems (TDS)[2] regarding the pharmaceutical development and quality information to include in new drug applications (NDAs) and abbreviated new drug applications (ANDAs).[3,4] Specifically, the guidance discusses FDA's current thinking on product design and pharmaceutical development, manufacturing process and control, and finished product control. It also addresses special considerations for areas where quality is closely tied to product performance and potential safety issues, such as adhesion failure and the impact of applied heat on drug delivery.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. General

[1] This guidance has been prepared by the Office of Pharmaceutical Quality and Office of Generic Drugs in the Center for Drug Evaluation and Research, in consultation with the Center for Devices and Radiological Health, and the Office of Combination Products, at the Food and Drug Administration.

[2] For the purpose of this guidance, both *transdermal* and *topical delivery systems* are referred to by the acronym "TDS."

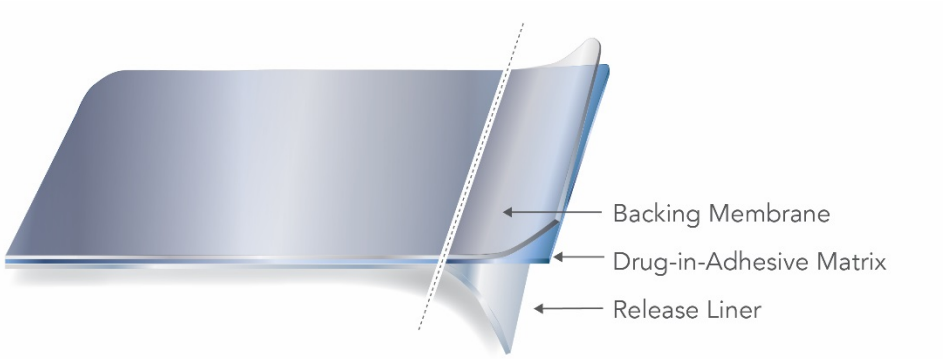
[3] Some TDS (such as microneedles, active transport TDS, reservoir TDS, and TDS applied to broken skin) have other considerations that are not addressed in this guidance.

[4] The general principles in this guidance can also be applied to nonapplication drug products; for example, over-the-counter drugs products marketed under the monograph regulatory construct (see 21 CFR part 330).

Transdermal delivery systems are designed to deliver an active ingredient (drug substance) across the skin and into systemic circulation, while topical delivery systems are designed to deliver the active ingredient to local tissue.[5] Both delivery systems present similar manufacturing and quality control concerns and similar risks to patients. TDS can be broadly divided into matrix type and liquid or gel reservoir type delivery systems.

Matrix type TDS contain one or more active ingredients dissolved or partially suspended in a mixture of various components, including adhesives, penetration enhancers, softeners, and preservatives, and are typically manufactured using solvent, hydrogel, or hot melt-based practices. An example of a matrix type TDS is shown in Figure 1, but matrix TDS may include additional layers and/or more complex designs.

Figure 1. Matrix Type Transdermal or Topical Delivery System

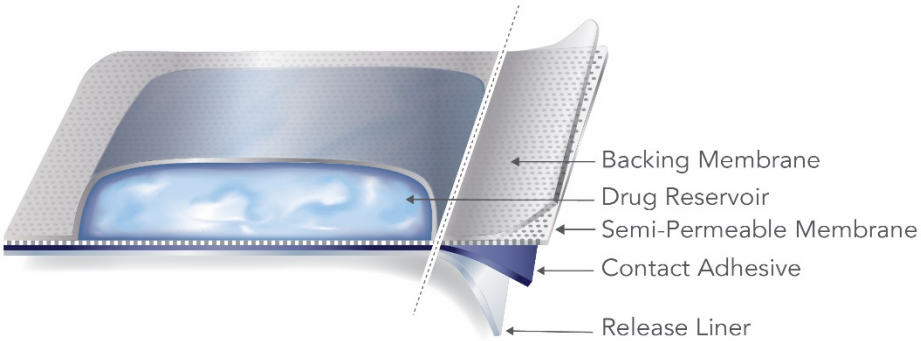


Reservoir type TDS similarly contain a variety of components in liquid or semi-solid form; however, reservoir type TDS utilize a heat-sealed area to entrap the active gel between the backing membrane and a microporous membrane. An example of a reservoir type TDS is shown in Figure 2. Because of the inherent failure modes and safety risks associated with the reservoir TDS, FDA recommends TDS manufacturers and applicants focus development efforts on matrix type TDS.[6]

[5] Topically administered liquid and semi-solid drug products without a carrier device (e.g., gels, creams, lotions, foams, ointments, or sprays) are not considered to be TDS and are not covered by this guidance, even though they can be formulated to provide local, or in some cases, transdermal delivery of the drug.

[6] Applicants are strongly encouraged to consult the Office of Pharmaceutical Quality early in the development process prior to pursuing a reservoir design.

Figure 2. Reservoir Type Transdermal or Topical Delivery System



B. Regulatory Status

Transdermal and topical delivery systems are combination products as defined by 21 CFR part 3, and must comply with 21 CFR part 4 subpart A (Current Good Manufacturing Practice Requirements for Combination Products). Within 21 CFR part 4, there is description of how requirements from 21 CFR parts 210 and 211 (drug CGMPs) and 21 CFR part 820 (device Quality System regulation) apply to combination products.[7]

In particular, design controls (21 CFR part 820.30) apply to drug-device combination products including TDS.[8] Essentially, design control activities should confirm that there are no negative interactions between constituent parts and assure that their combined use results in a combination product that is safe and effective and performs as expected. Guidance for industry on pharmaceutical development also addresses product design and development procedures,

[7] For related guidance, see FDA guidance for industry and staff *Current Good Manufacturing Practice Requirements for Combination Products* (January 2017). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.[8] As can be the case for components of other single-entity combination products, some components of TDS may be treated as components of both the drug and device constituent parts of the combination product. Because the purpose of this guidance is to offer technical recommendations relating to product development and assessment, we use the general term "component(s)" throughout the guidance to avoid unnecessary complexity regarding such incidental regulatory issues.[9] See FDA guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009). We reference International Conference for Harmonisation (ICH) guidelines, which address complex scientific issues or set forth first interpretations of regulatory requirements, and correspond to FDA draft and final guidance documents, respectively.

[8] As can be the case for components of other single-entity combination products, some components of TDS may be treated as components of both the drug and device constituent parts of the combination product. Because the purpose of this guidance is to offer technical recommendations relating to product development and assessment, we use the general term "component(s)" throughout the guidance to avoid unnecessary complexity regarding such incidental regulatory issues.[9] See FDA guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009). We reference International Conference for Harmonisation (ICH) guidelines, which address complex scientific issues or set forth first interpretations of regulatory requirements, and correspond to FDA draft and final guidance documents, respectively.

reflecting quality by design principles.[9] While quality by design and design controls share similar characteristics and goals, the device Quality System regulation (21 CFR part 820) includes specific requirements for design development that manufacturers must satisfy.[10]

It may be possible to leverage many aspects of pharmaceutical development as described in International Conference for Harmonisation ICH Q8(R2)[11] to achieve compliance with design controls. For example, the Quality Target Product Profile (QTPP) (see section III.A. below) is similar to "design inputs" (21 CFR part 820.30(c)), which ensure that design requirements are appropriate to address the intended use of the product. Further, studies conducted to verify that the critical quality attributes (CQAs) are met in the finished product may also address requirements for design "verification" and "validation" (21 CFR part 820.30(f), (g)), which ensure that the product's "design outputs" (21 CFR part 820.30(d)) result in a product that safely and effectively achieves its intended effects).[12]

III. TDS PRODUCT DEVELOPMENT

The following section provides an overview of considerations for product and process development, described from a pharmaceutical development perspective. As described above, development of a TDS product must also be compliant with design controls (21 CFR part 820.30). We recognize that the terminology used in 21 CFR part 820.30 can differ from that used in a particular pharmaceutical development program. Where pharmaceutical development practices are leveraged and built upon to demonstrate compliance with design controls for a TDS product, applicants should be able to communicate to FDA how the terminology they use relates to design control principles and requirements.

A. Quality Target Product Profile

Prior to TDS development, the applicant should establish the desired quality target product profile (QTPP). The QTPP is a prospective summary of the quality characteristics of the TDS product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the product (ICH Q8(R2)). In general, QTPP elements and their quality considerations for TDS may include:

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[9] See FDA guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009). We reference International Conference for Harmonisation (ICH) guidelines, which address complex scientific issues or set forth first interpretations of regulatory requirements, and correspond to FDA draft and final guidance documents, respectively.

[10] For example, requirements under 21 CFR part 820 for design control, purchasing controls, management responsibility and corrective and preventive action must be met. See FDA guidance for industry *Current Good Manufacturing Requirements for Combination Products* (January 2017) for additional information regarding options for complying with the requirements of 21 CFR part 820 for a combination product.

[11] See footnote 9.

[12] Additional requirements for design control include preparation of a design plan (21 CFR part 820.30(b)) and holding review meetings with specified personnel in attendance (21 CFR part 820.30(e)). See *Current Good Manufacturing Requirements for Combination Products* for additional information regarding design control requirements for combination products and other CGMP requirements for combination products that include a device constituent part.

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, physical design (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

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 population is pediatric.

B. Critical Quality Attributes

1. TDS Product

Early in the TDS development process, the applicant should generate a list of potential CQAs. A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (ICH Q8(R2)). Knowledge of the QTPP for the product, in combination with prior knowledge, risk assessments, and/or experimentation, can be used to develop the list of product CQAs. Each CQA, either alone or in concert with one or more other CQAs, should relate to one or more elements of the TDS product QTPP. The list of product CQAs can be modified as product development progresses and new knowledge is gained. The CQAs of the drug substance(s), excipients, components and container closure system should also be identified in the application.

For TDS, CQAs typically include appearance (such as lack of visible crystals), dimensions, uniformity of dosage units, 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

Selection of a drug substance should be justified based on the physicochemical and biological properties of the drug substance that can influence the performance of the TDS product and its manufacturability. In particular, properties that influence the rate of delivery, such as molecular weight, melting point, partition coefficient, pKa, aqueous solubility, and pH, should be considered. Other characteristics of the drug substance such as particle size, crystal form, and polymorphism should be evaluated and justified in terms of product performance.

3. Excipients and Components

Excipients and components used in TDS can include various adhesives, permeation enhancers, rate controlling or non-rate controlling membranes, solubilizers, plasticizers/softeners, or tackifiers, all of which can influence the quality and performance attributes of TDS.

Rigorous qualification of key excipients and components is important to ensure optimum product quality attributes in transdermal and topical formulations, and facilitates the postapproval change process for changes in the raw materials, manufacturing process, or suppliers.

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

- For adhesive polymer(s) as raw material(s): molecular weight, polydispersity, spectroscopic analysis (e.g., infrared radiation (IR) absorption), thermal analysis, intrinsic or complex 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 properties of an adhesive as raw material (e.g., rheology, including intrinsic viscosity and complex viscosity) can impact the final product quality attributes. Adhesive suppliers' specifications are often wide; thus, adhesive raw material received throughout the life cycle of the product may vary greatly within the adhesive suppliers' specifications. For example, the rheological properties of the adhesive lots used in the pivotal in vivo trial for TDS (e.g., bioequivalence (BE), Pharmacokinetic (PK), adhesion studies) may not be consistent with the supplier's previously manufactured adhesive lots or their future adhesive lots. Therefore, applicants should request historical rheology values from the adhesive manufacturer to better understand their process capabilities and the potential influence of variability in the adhesive

rheology on the final product. This can further assist applicants in assessing the need to establish or tighten internal controls for the raw material.

Identifying, evaluating, and properly controlling similar quality attributes of other key components of TDS products will enhance product and process understanding of the TDS throughout its life cycle.

4. Identifying Labeling

Applicants are encouraged to incorporate a representative label early in development to assure the labeling 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 for secondary 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 adequate contrast and remains visible for the duration of system wear and after disposal.

C. Product and Process Development

The principles of quality by design (QbD) and elements of pharmaceutical development discussed in ICH Q8(R2), Q9, and Q10[13] should be applied throughout the TDS life cycle to ensure TDS products have the identity and strength, and meet the quality and purity characteristics required under section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

TDS can be as simple as a single drug substance dissolved in a single adhesive, or highly complex, multi-component, multi-adhesive, multi-laminate matrices. Excipients and components in TDS can include various adhesive systems, permeation enhancers, rate controlling or non-rate controlling membranes, solubilizers, plasticizers/softeners, or tackifiers.

As a general principle, product development strategies should seek to minimize product complexity while still achieving the QTPP. Less complex products are likely to have fewer potential failure modes than more complex products. Product and process controls can be simplified as product complexity decreases, which can reduce the risk of manufacturing problems occurring during routine commercial manufacture.

[13] See FDA guidances for industry *Q8(R2) Pharmaceutical Development* (November 2009), *Q9 Quality Risk Management* (June 2006), and *Q10 Pharmaceutical Quality System* (April 2009).

Systematic quality risk assessments and process characterizations can support the identification of appropriate controls for manufacturing process variables, in order to produce TDS products with acceptable CQAs. Risk assessments can also help define the robustness of certain critical material attributes (CMAs) and critical process parameters (CPPs), such as raw material characteristics, hold times and equilibration periods.

IV. INFORMATION TO BE SUBMITTED IN AN APPLICATION

An applicant must provide technical data and information in sufficient detail to permit the Agency to make a knowledgeable judgment about whether to approve the application or whether grounds exist under section 505(d)[14] or 505(j)[15] of the FD&C Act to refuse to approve the application. This includes information about the drug substance[16] and information about the TDS product.[17]

The following sections provide recommendations to applicants about pharmaceutical development and quality information to be included in the application sections described in ICH M4Q.[18]

A. Pharmaceutical Development

As described in ICH M4Q, section 3.2.P.2 of the application should contain information on studies conducted to establish that the dosage form, formulation, manufacturing process, container closure system, microbiological attributes, and usage instructions specified in the application are appropriate for the intended use of the TDS product. The applicant should address the following:

- A description of the QTPP.

- A list of the CQAs of the TDS product, along with the limit, range, or distribution associated 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 (as appropriate), 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.

[14] See 21 CFR part 314.50(d).
[15] See 21 CFR part 314.94(a)(9).
[16] See 21 CFR parts 314.50(d)(1)(i) and 314.94(a)(9).
[17] See 21 CFR parts 314.50(d)(1)(ii) and 314.94(a)(9). Please note information about the combination product as a whole (referred to as TDS product in this guidance) should be provided in those eCTD sections intended for the drug product alone.
[18] See FDA guidance for industry *M4Q: CTD — Quality* (August 2001).

261
262 - Applicants should specify the allowable ranges around the process parameters and
263 material attributes that have a potential to impact TDS product CQAs with
264 justification and describe how they will be monitored.
265
266 • A description of the quality risk assessments, potential failure modes, and product and
267 process control strategies.
268

1. Batch Formula

For processes that use solvated raw materials, batch formulas should be designed to tolerate variation in the solvent content of raw materials. Drug substance overages and excipient excesses can be added to a batch to account for evaporation during drying, but the amount of overage or excess should be controlled and justified by process development studies. Applicants should describe any cross-linking reactions since these reactions impact the chemical composition and quality of the finished product.

2. Expectations for Registration/Exhibit Batches

Applicants should submit data for registration/exhibit batches manufactured from three distinct laminates, where each laminate is made using different lots of drug substance, adhesives, backing, and/or other critical elements in the TDS product. Release and stability sampling should be representative of the full length and width of the laminates to demonstrate that the manufacturing process is robust.

Any clinical batch (e.g., those used in phase 3, PK, BE, adhesion, or irritation and sensitization studies) should be included in the formal stability program.[19,20] Applicants should provide the executed batch records and certificates of analysis for all batches used in clinical and BE studies, including placebo batches. Placebo batches should include all inactive ingredients and components and representative printing.

Applicants should report the actual yields, theoretical yield, and percentages of theoretical yield from the conclusion of each appropriate phase of manufacturing, processing, packaging, and holding. The theoretical yield should be calculated for each batch prospectively. For example, if a coating process is stopped due to a manufacturing issue, the theoretical yield should be based on the mass that was intended to be coated rather than the mass that was actually coated. The yield for TDS processes may be lower than the usual yield for many other drug manufacturing processes. However, abnormally low yields in the TDS submission batches should be explained in the application.

Because of the sensitivity of TDS products to small differences in manufacturing process, a master table comparing the clinical, BE, registration/exhibit, and proposed commercial batches should be included in section 3.2.P.2.3 of the application. For each batch, this table should specify the manufacturing process used (including equipment, and manufacturing scale, and those parameters that could directly or indirectly impact a CQA), and the results of critical in-process tests (specifying the test procedure and acceptance criteria), yield, and reconciliation data. The table should also include links to any information referenced from other parts of the submission. It should also clarify whether these batches were packaged to completion at the die cutting and pouching stage.

[19] See FDA guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products*.

[20] See FDA guidance for industry *ANDAs: Stability Testing of Drug Substances and Products: Questions and Answers* (May 2014).

3. Product Characterization Studies

Because of the uniqueness of the TDS dosage form, specialized developmental studies and evaluations 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 saturation of 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 with relevant 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. For transdermal systems, the strength can be derived from and supported by either PK data or by residual 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 (C_{ss}) at the steady state. The second approach involves the measurement of the amount of drug left in the transdermal systems at the end of the wear period and dividing the "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 Drug Delivery 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 the application. To provide a robust analysis of the residual drug, we recommend the following:

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 should be 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 skin during 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 of three 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 should also 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 the amount 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 to characterize 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 during IVPT model development:

- Selection of the diffusion apparatus and the operating conditions like stirring rate or flow rate, as well as temperature control to maintain the under-normal-conditions skin surface temperature (32°C ±1°C)

- 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 protocol should specify the nominal skin thickness and its range, details of the skin barrier integrity test, and any occlusion of the product during the IVPT. Visual observations alone are not sufficient to characterize the barrier integrity of the skin. Acceptable barrier integrity tests may be based on tritiated water permeation, trans-epidermal water loss (TEWL), or electrical impedance/conductance measured across the skin. The test parameters and acceptance criteria used for the skin barrier integrity test should be justified based on relevant literature references or other information.

The IVPT protocol should also include details about the receptor solution, system equilibration, procedures for skin mounting and application of the TDS, as well as any measures to secure the TDS on the skin surface to prevent lifting. We recommend that an antimicrobial agent be included in the receptor solution (e.g., ~0.1 percent sodium azide or ~0.01 percent gentamicin sulfate).

The IVPT study report should include dose duration, sampling duration, sampling time points, concentration of samples, concentration of the antimicrobial component, and the empirical stability (at relevant temperatures) and solubility of the active ingredient in the receptor solution. The study report should also include the number of individuals whose skin was evaluated (i.e., skin donors) and the number of replicate skin sections per donor per treatment group.

All treatment groups compared in an IVPT study should be dosed on the skin samples from the same set of donors, with the same number of replicates per donor per treatment group. These treatment groups should also use the skin samples from the same anatomical site from all donors, unless varying these parameters is essential to the design of the study and the evaluation of the TDS. The study report should include the equilibrated skin surface temperature prior to dose application, and the ambient temperature and relative humidity in the laboratory, as well as the extent of qualification of the sample analytical methods (e.g., HPLC).

g. Extractable and Leachable Testing

All TDS should be evaluated for potential compounds that could be transferred from the product to the patient. This evaluation should include assessments of extractables and leachables, consistent with USP <1663> and <1664>.

As defined in United States Pharmacopeia (USP)[21] General Chapter <1663> *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems*, "extractables are organic and inorganic chemical entities that are released from a pharmaceutical packaging/ delivery system, packaging component, or packaging material of construction and into 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 <1664> *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems*, "leachables are foreign organic and inorganic entities that are present in a packaged drug product because they have leached into the 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."

In the context of this guidance, extractable impurities are chemical entities that can be drawn out of the backing membrane, release liner, pouching material, printed ink, internal membranes, and components other than the drug substance and adhesive matrix by a solvent system. Additionally, an extraction study can detect compounds introduced into the TDS from the

[21] USP references in this guidance refer to USP 41–NF 36.

manufacturing process, which can impact the final impurity profile of the TDS product. In the context of this guidance, leachables are chemical entities present in a packaged TDS because they leached into the adhesive matrix (or where applicable, reservoir) under normal conditions of storage or during accelerated stability studies. These compounds may transfer from the adhesive matrix (or reservoir) to the patient during use.

Extractable studies are used to inform the leachable study design. The leachable data should be correlated, if possible, with the extractables profile(s) determined under the various control extraction 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[22]), unless otherwise justified. For some products, the maximum daily dose may require applying more than one TDS.

Adhesive impurities such as residual monomers, initiator byproducts, and aldehydes are not considered extractables or leachables because these impurities are present at peak concentrations before product manufacture. Control of adhesive impurities is discussed elsewhere in this guidance (see section IV. INFORMATION TO BE SUBMITTED IN AN APPLICATION, C. Control of TDS Product). However, the leachable studies discussed below may be leveraged to justify adhesive impurity limits or as part of the toxicological risk assessment for adhesive impurities because a leachable study is performed on the proposed commercial product.

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

i. Extractable Studies

Extractable studies should be conducted early in the pharmaceutical development process to understand the potential leachables from components of the proposed commercial TDS. These studies should be conducted on components such as backing membrane, release liner, rate controlling or other internal membranes, ink and pouching. The testing components should be extracted in a variety of solvents with a range of polarities under vigorous laboratory extraction conditions to maximize the levels of extractables and identify as many potential leachables as possible. One of the extraction solvents used in the extractable studies should include the solvent of the proposed commercial adhesive(s) platform or the known residual solvents for the finished TDS. The choices of solvents used should be justified.

ii. Leachable Studies

The conditions of the leachable studies should mimic as closely as possible the "worst-case" clinical conditions of the skin (e.g., sweating during rigorous exercise). The solvent/solution selection (such as salt concentrations), temperature, level of agitation, duration of exposure to the solvent, etc., selected for the studies should be justified. The release liner should be removed

[22] See FDA guidance for industry *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk* (March 2018).

from the system during the study to adequately expose the adhesive layer to the biologically relevant solvent. Applicants should conduct a multi-timepoint leachable analysis (e.g., 0, 6, 12, 24 months) to provide a comprehensive leachable profile and identify any trends in leachables as these data could impact the shelf life of the product. 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 distinct laminates of TDS placed on stability testing.

h. Assessing the Effects of Heat

Heat from external sources such as a heating blanket, and potentially from a rise in internal body temperature due to strenuous exercise or fever, may affect the rate of drug release from the TDS and the absorption of drug into and through the skin. We recommend that applicants study the impact of an elevated TDS/skin surface temperature on the delivery profile of TDS relative to its delivery profile at a normal TDS/skin surface temperature.

For a TDS product to be submitted in an NDA, we recommend that the heat effect studies be conducted as part of a clinical study using the proposed commercial product. In designing the heat effect studies, critical factors such as appropriate elevated test temperature(s), heat exposure onset time(s), duration(s), and cycles (if any), as well as mechanisms of heat exposure (e.g., heating lamp, heating pad, etc.) should be identified.

For a TDS product to be submitted in an ANDA, the applicant should evaluate whether the test TDS, used under elevated temperature conditions, increases drug delivery compared 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 study with a sufficient number of donors and replicates per donor per treatment per temperature condition is recommended to obtain meaningful data. A study with fewer than four donors and four replicates per donor per treatment per temperature may be difficult to interpret.

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

1. BASELINE: Both the test and R products should be maintained at a TDS/skin surface temperature 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 for a period thereafter, which may be the remainder of the study duration.

It should not be assumed that a set temperature for a circulating water bath will provide the target temperature at the TDS/skin surface. The TDS/skin surface temperature should be directly measured using an infrared thermometer or other temperature probe. The study duration for a 7-day wear TDS need not encompass the entire labeled duration of wear. It may be adequate to perform an IVPT study for a 48 or 72 hour duration, if that duration is sufficient 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

Due to complexities of many TDS formulations, adhesive matrices often do not form true solutions, rather they manifest as dispersions. If rearrangements of the dispersed-like system occur over time within the matrix, they can possibly lead to lack of adhesion or changes in drug delivery and release. As such, it is important to have a good understanding of the TDS formulation, the way the drug substance and excipients are dispersed within the adhesive matrix, and the tendency of the matrix to change over time from product release through its expiry period. Therefore, it is informative to assess surface and cross-sectional changes in the TDS matrix throughout the shelf life of the developmental batches using high-powered microscopy, elemental mapping, or other appropriate tools. These tools may not be appropriate for every TDS; applicants should provide a scientific justification for the tools used. These assessments will help achieve comprehensive understanding of product and process, mitigate quality-related risks, and assure that the TDS meets the requisite quality attributes through its expiry period.

4. Proposed Manufacturing Changes

Scale-up proposals and other process changes may be proposed in an original NDA or ANDA, but the level of additional information needed to support these changes will generally be commensurate with the risk of the change to adversely impact product quality. In general, changes to TDS after the conduct of pivotal clinical studies should be avoided when possible because of the sensitivity of TDS to small changes in formulation and manufacturing process.

Low-risk changes may be adequately supported with updated master batch records and batch formulas. Examples include scale-up of solvent-based and aqueous mixtures within a factor of 10 using equipment of the same design and operating principles, or proposing a change to converting and pouching equipment of the same design and operating principle.

Moderate-risk changes may warrant additional developmental studies and stability data on commercial scale batches to demonstrate that they will not result in an adverse impact on the quality of the product. Examples of such changes may include scale-up of hot-melt mixtures within a factor of 10, scale-up of screw-based mixing processes, and changes to coating/drying/laminating equipment of the same design and operating principle.

Changes that pose a high risk to quality may warrant additional in vivo studies. An example is changing the manufacturing process to incorporate equipment of a different design and operating principle.

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 detailed schematic diagram of the proposed production process, including descriptions of the equipment, operating conditions, and process controls, should also be provided.[23]

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 life cycle.

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 operation and 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: Mixing operations produce bulk mixtures for the coating step. Mixing can impact CQAs such as assay, stability of drug substance and/or excipients, content uniformity, microscopic appearance, and physical properties of the adhesive. 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 should be justified, as necessary, based on development studies. CMAs that can impact mixing include drug substance particle size, polymorphic form, raw material rheological attributes, and percent solids for materials supplied in solvent-based mixtures.

- Coating, drying, and lamination: Coating is the application of a mixture to a substrate. Depending on the equipment used, coating can impact CQAs such as content uniformity and microscopic appearance. Though CPPs are equipment dependent, firms should demonstrate that the control strategy (e.g., process parameters to be controlled) is adequate to ensure content uniformity and microscopic appearance for the full duration of the coating operation. CMAs that can impact coating include the rheology of the bulk mixture and within-roll uniformity of the substrate to be coated.

  Drying involves the removal of solvent from the mixture following the coating process. This process 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 considered during process development include line

[23] See 21 CFR part 314.50(d)(1)(ii)(c).

speed, the pump or screw speed, zone temperatures, air flow rates, temperature of the drying air, and humidity of the 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-controlling membrane.

- Slitting and Printing: The bulk product is typically slit longitudinally into narrower rolls of laminate for further processing. Slitting and printing are typically low risk steps; however, if certain aspects of the printing processes, e.g., excessive penetration depth or heat input, can adversely affect product quality, then printing processes should be characterized and controlled.

- Converting and pouching: Converting and pouching typically involve cutting a continuous laminate into individual units and sealing the unit in a heat-sealed pouch. CQAs affected by these processes include usability of the product (e.g., the ability to remove a release liner) and pouch integrity. Common CPPs for these steps include heat sealing temperatures and dwell times.

- Curing: Some TDS have processing steps to complete a curing reaction after drying or pouching. Curing time and curing conditions are common CPPs for this step. Curing should be completed before batch release testing if curing could impact test results.

- Hold times: Hold times must be defined and justified for in-process materials held between unit operations (21 CFR part 211.111). Applicants should use a risk-based approach to determine which CQAs to monitor during hold time studies.

- Other considerations: Tubing and other product-contact equipment must be qualified as non-reactive, non-additive, and non-absorptive (21 CFR part 211.65(a)). The selection of the tubing and certain product-contacting equipment should be risk-based, i.e., dependent on the duration of contact, process temperature, solvent system, material considerations, clearance of leachables during manufacturing, and clinical use considerations.

In-process controls (IPCs) for TDS are an integral part of the control strategy. The description of the proposed IPCs should address the following:

- At the mixing stage, IPCs can provide assurance of assay, viscosity, uniformity, and pH for aqueous mixtures. If multiple samples are taken from a dispersed mixture,

applicants should specify the mean, range for individual samples, and percent relative standard deviation.

- IPCs for coating, drying, and lamination can provide assurance of uniformity across the laminate and throughout the run. For example, measurements for film appearance, coat weight, and/or a test for residual solvents may be applicable IPCs for coating and drying. Film appearance measurements that allow detection and rejection of defects affecting continuity of an adhesive laminate (e.g., streaks) should be described in the application. Additionally, for films that are dispersions at the microscopic scale (e.g., acrylic adhesive dispersed in silicone, povidone dispersed in silicone, or solid drug substance dispersed in adhesive), applicants should describe the IPCs established to monitor uniformity throughout a coating run in the application. Samples for testing coat weight and uniformity should be representative of the full length and width of a laminate. Alternatively, these attributes can be monitored continuously (e.g., by the use of in-line coating measurement tools). In cases where the upstream controls can be used to confirm certain finished TDS specifications, such as residual solvents and residual adhesive impurities, IPC testing can be used in lieu of release testing for these attributes.[24]

- For converting and pouching, IPCs can provide assurance of pouch integrity, product placement within the pouch, and product appearance (e.g., adequacy of the printed label, die-cuts, and kiss-cuts). An automated system can perform in-process checks for product appearance in lieu of human operators if the automated system is demonstrated to be suitable for the intended task(s).

C. Control of TDS Product

Section 3.2.P.5 of the application should contain the following information on control of the 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

[24] See *Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance - Records and Reports* at the following site: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124787.htm.

- 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[25]
- Moisture content, when applicable
- Residual solvents

The proposed analytical procedures should be documented in sufficient detail that they can be reviewed and reproduced in FDA laboratories. In some cases, if upstream controls can be used to confirm that a batch of product meets a CQA listed on the specification, that attribute may not need to be tested at release for every batch, but should be indicated as such on the specification.[26] Applicants proposing a control strategy using such an approach should provide justification.

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

a. Adhesive Impurities

Adhesives may contain residual monomers, initiator byproducts, aldehydes, etc. The safety of these compounds should be assessed, as some of these compounds are classified as neurotoxic (e.g., tetramethylsuccinonitrile) or mutagenic (e.g., crotonoaldehyde). Manufacturers are encouraged to contact the raw material suppliers to discuss the selected adhesive raw material and all potential impurities, as some impurities may not be reported on the certificates of analysis provided by the supplier. Applicants should discuss the potential impurities arising from the raw material in the application. A control strategy for any impurity of toxicological relevance should be established and justified. The control strategy may include testing at the raw material stage, demonstrating that the manufacturing process is capable of consistently removing the impurities of concern, testing of the final laminate, or a combination of the above.

To support a proposed control strategy based on the capability of the manufacturing process to consistently remove any impurities of concern, applicants should provide data to demonstrate a reduction in the level of the impurity in the final laminate (or finished product) compared to the

[25] When applicable, we recommend manufacturers assess the risk of microbiological contamination to their TDS in order to establish the appropriate microbiological tests, specification, and manufacturing operations for their product. Based on this risk assessment, manufacturers should leverage existing approaches (ICH guidelines, USP standards, FDA guidance, etc.) to determine the testing necessary for their product.

[26] See FDA guidance for industry *Q8(R2) Pharmaceutical Development*.

level in the same batch of raw material.These data are necessary to quantitatively demonstrate effectiveness of the manufacturing process in removing the impurity and to establish controls for adhesive impurities based on levels in the raw material rather than on the final product.

Applicants may consider leveraging the leachable study discussed in the pharmaceutical development section of this guidance by testing adhesive impurities in the leachate. The leachable information can be used to provide toxicological justification for impurity limits or the information can be included as part of the toxicological risk assessment.

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 also be 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 throughout stability. 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 vivo correlation.

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

Using currently available methods, in vitro adhesion testing does not correlate to in vivo adhesion, but in vitro adhesion testing can be useful for quality control (QC) purposes. In vitro adhesion testing should include peel adhesion, release liner removal, tack, and shear (dynamic or static).[27] There are multiple methods and different experimental parameters for each of the tests.

The peel adhesion test measures the force required to remove (peel away) a TDS that has been applied to a standard test panel (e.g., polished stainless steel). The measurement of peel adhesion is influenced by the test parameters such as dwell time, substrate (e.g., stainless steel, high density polyethylene (HDPE)), peel angle, and peel speed.

A release liner peel test measures the force required to separate a TDS from its release liner. The measurement of release liner peel is influenced by experimental parameters such as peel angle and peel speed.

The probe tack test measures the force required to separate the test probe from the adhesive of the TDS. Tack measurement is influenced by the test parameters such as the contact area, the contact pressure, the time of contact (or dwell time), and rate of separation.

There are two categories of shear testing, namely dynamic and static. In the dynamic test, the TDS is pulled from a standard test panel (e.g., polished stainless steel). Dwell time, speed, type of test panel, mode of failure, and sample size are the typical test parameters reported for the

[27] See USP 41–NF 35 General Chapter <3> *Topical and Transdermal Drug Products-Product Quality Tests.*

dynamic shear test. In the static shear test, the TDS sample is applied to a test panel that is at an angle 2° from the vertical, and the sample is subjected to a shearing force by a means of a given weight (e.g., 1000 g) suspended from the TDS; the time required to detach a standard area of the TDS from a stainless steel test panel under a standard load is measured. Dwell time, weight used, type of test panel, mode of failure, and sample size are the typical test parameters reported for the static shear test. The time taken for the TDS sample to detach from the test panel is also reported.

e. Cold Flow

Cold flow is the creeping or oozing of the adhesive matrix beyond the perimeter of the backing membrane or through the release liner slit. Cold flow may be present on the TDS, release liner, pouch, or disposable films (sometimes termed slip sheets or protective films, such as a film over the backing and a film over the release liner). Though a quantitative method of assessing cold flow can provide a meaningful measurement, it may not describe the difficulty in removing the TDS from the pouch or the protective films from the TDS. The most accurate cold flow assessment for TDS will likely come from a combination of product-specific quantitative and qualitative methods.

The test methods should be discriminating and scientifically justified. Manufacturers should propose product-specific acceptance criteria with justification supported by product development research.

f. In vitro Drug Release

USP General Chapter <724> 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 below along 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 Reciprocating Holder (Apparatus 7).

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

Sufficient detail and data should be included in the method development and validation report so the adequacy of the method for batch release and stability testing can be properly assessed. Examples of parameters to evaluate during method development include selection of USP apparatus/other equipment, drug release medium, rotation or agitation speed, temperature, pH, sink conditions, use of a surfactant, and other technical aspects of the test. An in vitro drug release method should be simple, reliable, reproducible, discriminating, and robust. Applicants should strive to develop a method that releases as much drug as possible.

The validation section of the report should include complete information/data regarding: i) the discriminating ability of the selected method, ii) the validation of the drug release methodology, and iii) the validation/verification of the analytical method selected to assay the drug release samples. The selected method should be able to differentiate the release profiles of TDS that are intentionally manufactured with meaningful variations in critical process parameters and formulation components. Validation data should demonstrate the range and sensitivity of the method for proportional drug release across different strengths of the TDS. In addition, validation data should demonstrate reproducibility of the method for drug release across different runs of the same batch and its robustness, i.e., its capacity to remain unaffected by changes in receptor medium temperature, paddle rate, and other method parameters.

The acceptance criteria for the in vitro drug release test should be based on the proposed TDS product 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 established by 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 terminal phases; 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 plateau should be considered 100 percent for the purposes of estimating the percent of drug release over time.

Wider acceptance criteria range for the drug release test may be acceptable if they are supported by an approved in-vitro in-vivo correlation model.

g. Crystal Presence

The presence of crystals or crystallization of the drug in the TDS over time can negatively impact the product performance. Therefore, it is important to establish a test and acceptance criteria to confirm the absence of crystals to be used at release and on stability. Microscopic and photometric methods are preferred rather than a simple visual count. It is recognized that some products are designed to be suspensions, however, this design does not preclude the need for a crystal specification. Suspension products should still include tests and acceptance criterion to ensure against crystal propagation, which may impact drug delivery or adhesion properties of the product.

h. Pouch Integrity

The pouch for a TDS is critical to the stability and integrity of the product. Pouch integrity testing should be conducted as part of finished product release unless justification is provided for an alternative approach that assures the finished product specification is met.

D. Additional Stability Studies

In addition to the standard battery of formal stability and photostability studies for drug substance and drug products discussed in ICH Q1A and ICH Q1B,[28] TDS applicants and manufacturers should conduct stability studies under challenge conditions that include temperature excursions, freeze/thaw, and/or crystal seeding. These additional studies are intended to address certain product quality issues such as crystal formation and growth. Moreover, in-use photostability testing may be appropriate to conduct for certain TDS formulations, depending on backing membrane opacity, duration of wear, and its expected exposure to light when in use.

V. SPECIAL TOPICS

A. Product Adhesion Considerations

In vivo adhesion studies provide the greatest prediction of adhesion, a CQA, for a proposed commercial product. Applicants should demonstrate that reasonable efforts were made to optimize adhesive characteristics of the TDS. This optimization should balance properties such as adhesiveness, cohesiveness, and stability to ensure a consistent and uniform adhesion of its entire surface area to the skin for the entire duration of wear. Applicants should develop a comprehensive strategy for assessing the adhesive attributes of the TDS. In vivo adhesion studies are necessary to demonstrate adequate adhesion of the TDS. Therefore, when possible, such as in efficacy studies for an NDA, subject diaries describing the actual in-use product adhesion performance should be used. This information bolsters adhesion data collected from the studies described below and in other guidances.[29]

Characterization of the adhesive properties of a TDS should demonstrate that the labelled uses are substantiated. For example, if the TDS is intended to be worn during bathing and showering, applicants should demonstrate that the TDS will continue to adhere during and after such incidental exposure to water. Product reinforcement, such as taping the edges or use of overlays, or occluding the product from water during bathing should not be permitted during the in vivo adhesion evaluation.

We recommend that when assessing the adhesion of a TDS, applicants use a 5-point numerical scale in which each score corresponds to a specified range of adhered surface area of the TDS, as follows:

0 = ≥ 90% adhered (essentially no lift off the skin)
1 = ≥ 75% to < 90% adhered (some edges only lifting off the skin)
2 = ≥ 50% to < 75% adhered (less than half of the TDS lifting off the skin)

[28] See FDA guidances for industry *Q1A(R2) Stability Testing of New Drug Substances and Product*s (November 2003), and *Q1B Photostability Testing of New Drug Substances and Products* (November 1996).

[29] See FDA draft guidance for industry *Assessing Adhesion with Transdermal Delivery Systems and Topical Systems for ANDAs* (October 2018). When final, this guidance will represent the FDA's current thinking on this topic.

3 = > 0% to < 50% adhered (not detached, but more than half of the TDS lifting off the skin without falling off)
4 = 0% adhered (TDS detached; completely off)

Additionally, the following information should be collected:

- At each time point when adhesion is assessed on the above described 5-point scale, the scorer should also record their actual percent adherence estimate (e.g., if the observer scores the product as a two on the five point scale and estimates that the product appears to be 60 percent adhered, a score of two and a 60 percent should be recorded for that time point).

- Photographic evidence showing the extent of TDS adherence to the skin at each time point should be provided.

B. Product Storage and Disposal – Labeling Considerations

TDS storage conditions should be supported by stability data and stated in the label. Generally, we recommend controlled room temperature for the storage of TDS. Excursions, if permitted, should be indicated on the label. The label should also state that TDS should not be stored outside of the pouch if that is necessary to preserve the safety, efficacy, and quality of the TDS.

Transdermal and topical delivery systems often contain post-use residual drug in the delivery system. Considering the therapeutic nature of the drug compound and potential adverse events resulting from unintended exposure, the instruction for product disposal should be clearly outlined in the labeling. It is important that the disposal process prevents exposure of the residual drug to the environment and/or other people. Depending on the nature of the product, special instructions may be required to prevent exposure to children and caregivers, which could result in significant safety-related consequences.