**Central Administration for Pharmaceutical Products**
**General Administration of Human Pharmaceuticals Registration**
**Administration of Technical Affairs for Human Pharmaceuticals**

# Notice to applicant

## Guidance on Atypical Active Pharmaceutical Ingredients for Medicinal Products

## Year 2026

**Code: EDREX: NP. CAPP.066**
**Version No: 3**
**Issue Date: 08-02-2026**
**Effective date (if needed): 08-02-2026**

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## 1. Introduction

This guidance aims to provide applicants with the required information for Atypical Active Pharmaceutical Ingredients (AAPIs) used in medicinal products and their drug master files` (DMF) requirements.

Atypical Active Pharmaceutical Ingredients (AAPIs) are “Substances which have been registered as the active ingredient in a medicine but whose primary industrial use is not as a pharmaceutical active substance”.

## 2. Scope

This guidance applies for any medicinal product containing Atypical Active Pharmaceutical Ingredients (AAPIs) submitted for evaluation of CTD Quality Module.

## 3. Abbreviations

3.1. AAPIs: Atypical Active Pharmaceutical Ingredients.

3.2. CTD: Common Technical Document.

3.3. TSE/BSE: transmissible spongiform encephalopathies / Bovine spongiform encephalopathy.

## 4. Definitions

4.1. Active pharmaceutical ingredient (API): Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form, and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

4.2. Drug master file (DMF): is a document containing information on an Active Pharmaceutical Ingredient (API) containing factual information on a drug product's chemistry, manufacture, stability, purity, impurity profile and packaging.

4.3. The Common Technical Document (CTD): is a set of specifications for a dossier to be submitted to the regulatory authorities for the registration/marketing authorization of medicines.

## 5. Main topic

- As Atypical Active Pharmaceutical Ingredients (AAPIs) are substances registered as the active ingredient in a medicine but whose primary industrial use is not as a pharmaceutical active substance, they have limited available data in their DMF. Most of them have conventional simple manufacturing process that unlikely to introduce impurities other than those already listed in the monographs. For that reason, this guidance focuses on the requirements of DMF of Atypical Active Pharmaceutical Ingredients (AAPIs).
- A list of Atypical Active Pharmaceutical Ingredients (AAPIs) is available on EDA Official Website.
- Hereafter, DMF Requirements for Atypical Active Pharmaceutical Ingredients.

| DMF sections | Required (R)/ Optional (O) | Notes |
|---|---|---|
| **3.2.S.1 General Information** | | |
| 3.2.S.1.1 Nomenclature | **R** | |
| 3.2.S.1.2 Structure | **R** | |
| 3.2.S.1.3 General Properties | **R** | |
| **3.2.S.2 Manufacture** | | |
| 3.2.S.2.1 Manufacturer(s) | **R** | |
| 3.2.S.2.2 Description of Manufacturing Process and Process Controls | **R** | Brief description with manufacturing process flowchart including materials used |
| 3.2.S.2.3 Control of Materials | **O** | |
| 3.2.S.2.4 Controls of Critical Steps and Intermediates | **O** | |
| 3.2.S.2.5 Process Validation and/or Evaluation | **O** | |
| 3.2.S.2.6 Manufacturing Process Development | **O** | |
| **3.2.S.3 Characterization** | | |
| 3.2.S.3.1 Elucidation of Structure and other Characteristics | **O** | |
| 3.2.S.3.2 Impurities | **R** | Brief description of possible impurities |
| **3.2.S.4 Control of Drug Substance** | | |
| 3.2.S.4.1 Specification | **R** | From both API manufacturer and finished product manufacturer |
| 3.2.S.4.2 Analytical Procedures | **O** | |
| 3.2.S.4.3 Validation of Analytical Procedures | **O** | |
| 3.2.S.4.4 Batch Analyses | **R** | Certificates of analysis (COA) |
| 3.2.S.4.5 Justification of Specification | **R** | |
| **3.2.S.5 Reference Standards or Materials** | | |
| 3.2.S.5 Reference Standards or Materials | **O** | |
| **3.2.S.6 Container Closure System** | | |
| 3.2.S.6 Container Closure System | **R** | Brief description only |
| **3.2.S.7 Stability** | | |
| 3.2.S.7 Stability | **O** | |

**Notes:**

1. Free TSE/BSE declaration is required.
2. Additional data may be required if deemed necessary.

## 6. References:

NA

## 7. Annexes:

NA

**Document History**

| Version number | Issue Date | Summary of Change |
|---|---|---|
| 1 | 24-08-2023 | New Issue |
| 2 | 03-08-2025 | Addition of two ingredients (Sodium Citrate & Potassium Bicarbonate) to the List of Atypical Active Pharmaceutical Ingredient (AAPI) |
| 3 | 08-02-2026 | Removing Annex I: List of Atypical Active Pharmaceutical Ingredient (AAPI) which is replaced by a published list of AAPI on EDA official website. |