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STRUCTURE OF CHEMICAL COMPOUNDS, METHODS OF ANALYSIS AND PROCESS CONTROL

STANDARDIZATION OF DRUG SUBSTANCES ACCORDING TO THE *PURITY* SECTION

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The current classification of impurities in chemical and mineral drug substances is presented. General approaches to standardization of chemical and mineral drug substances according to the *Purity* section are given depending on their origin and production technology and considering requirements of international and domestic pharmacopoeial practice.

Keywords: drug substances, impurities, purity, standardization.

Modern drugs are characterized primarily with respect to their compliance with requirements on quality, efficacy, and safety. According to World Health Organization (WHO) documentation, the quality of medicines is assessed from its compliance with quality standard requirements, which includes drug quality standards, in particular, a pharmacopoeial monograph and/or regulation or regulatory document (RD). According to Russian Federation law No. 61-FZ dated Apr. 12, 2010, "On Circulation of Medicines" (last revision dated Dec. 29, 2015), medicines include drug substances and drugs.

Drug substances are medicines in the form of active ingredients of biological, biotechnical, mineral, or chemical origin that possess pharmacological activity, are intended for manufacturing and preparation of drugs, and determine the efficacy.

According to this definition, drug substances can have various origins and exist in various aggregate states (Figs. 1 and 2), which accounts for their different quality requirements.

Thus, the quality of medicines, including starting drug substances of biological origin, is regulated by the general pharmacopoeial monograph (GPM) "Biological drugs" and other GPMs depending on the group and subgroup of this drug category. The quality of drug substances of plant origin is regulated by the GPM "Medicinal plant raw material. Drug substances of plant origin." The main requirements for drug substances of chemical and mineral origin are given in GPM 1.1.0006.15 "Drug substances," Quality requirements for an actual drug substance are given, as a rule, in the corresponding pharmacopoeial monograph (PM).

A PM is a document approved by the authorized federal executive organization and containing a list of quality indicators and drug quality control methods.

Quality indicators included in a PM and/or RD for a drug substance of chemical or mineral origin can be arbitrarily divided into three groups, i.e., identity, purity, and quantitation. Identity tests allow the compliance of the drug substance to its name to be confirmed. Quantitation of the content of main active ingredient in a drug substance can guarantee that the required pharmacological effect or efficacy of the drug is achieved. Purity tests of drug substances assure not only their efficacy in the drug but also its safety.

The purity of a drug substance is characterized primarily by the impurity profile and content. According to the WHO guideline on *Good Pharmacopoeial Practices*, the ICH Harmonised Tripartite Guideline *Impurities in New Drug Sub-*

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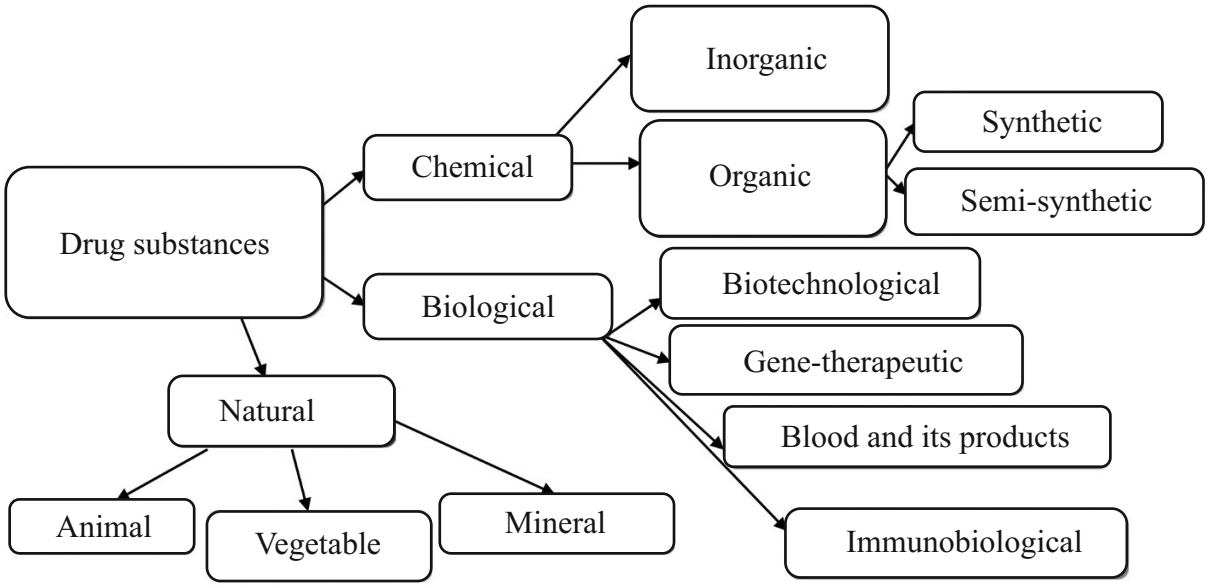

Fig. 1. Classification of drug substances according to origin.

stances (Q3A) [1] and Harmonised Guideline *Impurities: Guideline on Residual Solvents* (Q3C) [2], and others, impurities in drug substances can to a first approximation be subdivided into three main groups, i.e., organic impurities, most of which are related; inorganic impurities such as water; and residual organic solvents, biological impurities, and several others. It is noteworthy that organic drug substances typically contain all three impurity groups. However, inorganic impurities are lowest in them. Inorganic drug substances of both chemical and mineral origin contain primarily inorganic impurities, water, and, in several instances, residual organic solvents.

The commonly accepted classification of impurities subdivides them into general, which are characteristic of various substances, and specific, which are present because of the nature and production method of an actual drug substance. Furthermore, impurities can be allowed, in which case their contents are strictly regulated, or unallowed. The presence of unallowed impurities can not only decrease the pharmacological effect of the drug but also cause adverse side effects.

For example, Potassium Chloride drug substance for parenteral drugs is not allowed to contain sodium ions because they are antagonistic to the mechanism of action on myocardium.

As a rule, PMs or RDs for organic drug substances include tests for *Related impurities* that are intended to monitor related organic impurities [3] and are specific [4, 5]. Such impurities can be subdivided into two large groups, i.e., processing impurities from manufacturing and decomposition (degradation) products of the drug substance or impurities formed by various factors during storage, e.g., temperature, light, pH, or reaction with the primary packaging material.

Processing impurities include:

Starting materials or drug substances that are used to synthesize other drug substances. Obviously, they should be selected and checked, if possible, so that they have insignificant subsequent effects on the identity, purity, and quality of the drug substance.

Intermediates are organic compounds formed during the synthesis of drug substances. They include:

impurities resulting from rearrangements;
impurities resulting from *in situ* reactions;
reactive intermediates;
impurities of *bis*-compounds (dimer formation).

Side (accompanying) products (subproducts) are impurities with structures similar to that of the drug substance and include:

products from incomplete reactions;
unreactive products;
extended reaction products;
products from isomerizations;
products from undesired reactions between starting materials, intermediates, chemical reagents, or catalysts.

Transformation products of side products, including derivatives of side products.

Polymorphic forms.

Chiral impurities:
enantiomers;
diastereomers.

Reagents, ligands, catalysts, etc.

Decay (degradation) products of the drug substance that are generated during storage as a result of various chemical reactions and conditions such as:

-hydrolysis that affects, e.g., carboxylic acid derivatives; compounds containing functional groups sensitive to

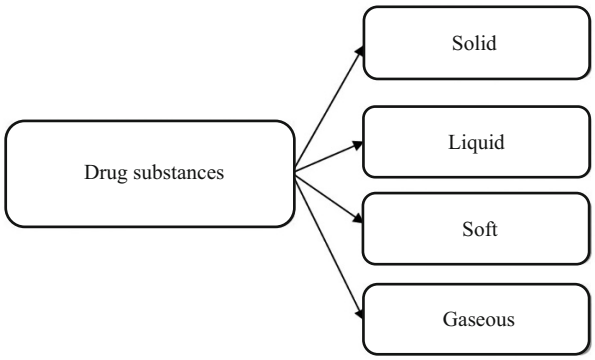

Fig. 2. Classification of drug substances according to state.

acid-base hydrolysis (e.g., acetylsalicylic acid, atropine, and chloramphenicol);

-*oxidation including* auto-oxidation resulting from chain and free-radical processes, e.g., methotrexate, adinazolam, catecholamines, conjugated dienes (retinol acetate), nitroso- and nitro-derivatives;

-*photolysis*, including cleavage of drug components by UV radiation (e.g., ciprofloxacin);

-*decarboxylation* or loss of CO_2 by carboxylic acids on heating;

-*extreme pH values* that cause acid- or base-hydrolysis.

-*reaction with packaging materials*.

Because chemical compounds can be synthesized and purified differently, international pharmacopoeial practice is tending to include the maximum possible number of impurities in monographs/PMs for drug substances so that a manufacturer can specify in them those impurities characteristic of the used synthetic or purification scheme when formulating RDs. Currently, the GPM *Organic impurities in drug substances and drugs* is being prepared for inclusion in the State Pharmacopoeia (SP) of the RF.

Stress tests are used to create a profile of all possible impurities in newly registered drug substances [6]. Such tests are multiply significant:

TABLE 1. Normalization Criteria for Allowed Heavy Metal Content

Daily dose, g/d	Treatment length, d	Introduction of *Heavy metal* parameter and established limit, ppm
> 0.5	< 30	*Heavy metal* parameter introduced, limit = 20
> 0.5	> 30	*Heavy metal* parameter introduced, limit = 10
< 0.5	> 30	*Heavy metal* parameter introduced. If the substance is intended for production of parenteral drugs, then the limit = 10; in other cases, 20.
< 0.5	< 30	*Heavy metal* parameter not introduced.

firstly, all possible decay products are identified;

secondly, decay pathways are defined;

thirdly, the stability of the drug substance molecule is evaluated.

Furthermore, stress tests facilitate the development of analytical methods for evaluating the stability and contribute to screening of potential genotoxins.

Effects on drug substances that should be studied during separate or combined stress tests include:

temperatures exceeding the storage temperature by increments of 10°C (e.g., 50, 60°C, etc.);

elevated moisture (e.g., relative humidity 75% and greater);

oxidation, if necessary;

photolysis, if necessary;

TABLE 2. Limiting Allowed Content in Medicines of Residual Organic Solvents for Toxicity Class 2

Solvent	Limiting content, mg/d	Limiting content, ppm
Acetonitrile	4.1	410
Hexane	2.9	290
N,*N*-Dimethylacetamide	10.9	1090
N,*N*-Dimethylformamide	8.8	880
1,2-Dimethoxyethane	1.0	100
1,4-Dioxane	3.8	380
1,2-Dichloroethylene	18.7	1870
Xylene	21.7	2170
Methanol	30.0	3000
Methyl butyl ketone	0.5	50
Methylene chloride	6.0	600
N-Methylpyrrolidone	5.3	530
Methylcyclohexane	11.8	1180
2-Methoxyethanol	0.5	50
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetrahydrofuran	7.2	720
Tetralin	1.0	100
Toluene	8.9	890
Trichloroethylene	0.8	80
Formamide	2.2	220
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3880
Ethylene glycol	6.2	620
2-Ethoxyethanol	1.6	160

hydrolysis over a broad pH range if the active ingredient is a solution or suspension.

Stress test conditions are harsher that those of accelerated stability tests.

Analytical methods for impurities must be selected correctly to provide reliable results. Developed methods should be sufficiently sensitive to determine low levels of significant impurities.

Spectroscopic methods are currently used most frequently to determine impurities and include UV and visible spectrometry, Fourier-transform IR spectrometry, NMR spectroscopy, and mass spectrometry (MS).

Total impurities are separated using TLC, GC, HPLC, capillary electrophoresis (CE), and supercritical fluid chromatography (SFC).

Hyphenated methods are used more and more often for separation and detection and include GC-MS, LC-MS (electrospray); LC-MS with a diode-array detector (DAD), LC-NMR, and LC-NMR-MS with a DAD.

Various preparative methods are used to isolate impurities and include solid-phase extraction, liquid extraction, enhanced extraction by solvents, supercritical fluid extraction, column chromatography, and flash chromatography.

The impurity profile created using these methods should specify all impurities in a single form to ensure any changes in them are controlled. The impurity profile should specify impurities related to the synthetic process and resulting from decay and/or reaction of the products.

Inorganic impurities include reagents, ligands, and catalysts; heavy metals or other residual metals; inorganic salts; other compounds (e.g., filtering materials, charcoal) [3]. As noted earlier, inorganic impurities are more characteristic of inorganic drug substances, especially of mineral origin, because natural minerals and other natural sources (e.g., iodine from oil-well flood waters) are prepared and purified subsequently using primarily inorganic acids, bases, salts, etc.

Inorganic-salt impurities can be subdivided into nontoxic and highly toxic anions and cations. Common cationic impurities are most often Na^+, K^+, NH_4^+, Ca^{2+}, and Ba^{2+}. Common anionic impurities are Cl^-, SO_4^{2-}, NO_2^-, and NO_3^-.

Impurities of other anions and cations are most often referred to as specific.

Determination of 15 anions and 17 cations is specified in various sections of the SP XIIIth Ed. The anions include carbonate, oxalate, peroxide, sulfate, sulfite, tartrate, ferrocyanide, phosphate, chloride, bromate, bromide, iodide, nitrate, nitrite, and sulfide. Cations comprise Al, Fe, K, Ca, Mg, Cu, Ag, Zn, Cd, Mn, Mo, Ni, Sn, Pd, Hg, Pb, and Cr.

Total heavy-metal and arsenic contents are regulated and determined by methods in the corresponding GPM [7, 8].

As a rule, the heavy-metal content should not exceed 0.001% if not otherwise indicated in the PM or RD.

Arsenic is determined if the starting material or production process of the drug substance could introduce As. As a rule, the As content should be <0.0001% [3]. However, if the RD contains other stricter regulatory requirements, the allowed toxicity of these compounds is evaluated based on a single, daily, and total dose of the drug. For example, Table 1 lists normalization criteria for the allowed heavy-metal contents.

Purified water or various organic solvents are used to purify drug substances by various methods, including recrystallization.

Water content is determined by the Fisher method (GPM *Water determination*). The water content is regulated and then strictly controlled.

Total ash or sulfate ash characterize the total mineralization of a drug substance. As a rule, sulfate or total ash should not exceed 0.1% [3].

Mass loss on drying or Water tests are used to control the contents of volatile compounds and moisture in the drug substance. Requirements for conducting the tests are regulated in the GPM *Mass loss on drying* and GPM *Water determination*. If the substance is not a crystal solvate, the mass loss on drying should not exceed 0.5 – 1.0%.

Residual organic solvents. This section indicates the names of organic solvents that are *used in the drug substance technological production process* and standards (allowed values) for their contents. The presence in the drug substance of other solvents at concentrations exceeding by 10% those regulated by the monograph signify that unregistered production technology was used to produce the drug substance. The determination of organic solvents in drug substances and standardization of their quantitative content are regulated by the GPM *Residual organic solvents* [9]. Most solvents are standardized considering their toxicity (Table 2).

Biological impurities include both pathogenic and nonpathogenic microorganisms, their metabolic products, and fungi. Natural semi-synthetic drug substances should be examined for virus safety and spongiform encephalopathy.

The following impurities are controlled according to a GPM:

microbiological purity;
sterility;
bacterial endotoxins;
virus safety;
spongiform encephalopathy etc.

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