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Standardization of the Active Pharmaceutical Ingredients Industrial Synthesis Technology

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Abstract

Literature data devoted to the modern principles of the quality assurance and safety of active pharmaceutical ingredients (APIs) industrial synthesis were analyzed. According to the quality by design concept, as well as Green Chemistry Principles, standardized approaches to the API industrial production quality assurance were offered. The main theses concerning development/selection/transfer of substances synthesis technology under pharmaceutical industry conditions were marked. The main criteria for selection a synthesis strategy of chemical substances, initial substances and solvents for the industrial synthesis of APIs were determined. A decision tree when selecting chemicals for their further use in APIs industrial synthesis technology was formulated and constructed. The basic stages and criteria of the process of pharmaceutical development were analyzed, and algorithm of development/transfer of API synthesis technology under industrial conditions, as well as its purification/crystallization was composed. Cause-and-effect diagram concerning the application of the Green Chemistry Principles in the industrial synthesis of APIs was built

Keywords**: **Standardization; Green Chemistry; Active pharmaceutical ingredients

Introduction

Production of active pharmaceutical ingredients (APIs) considered to be quite difficult worldwide [1], due to on the one hand it requires the use of chemical facilities that have a negative impact on the environment and on the other hand – it should ensure obtaining of chemical substances that consistently meet pharmaceutical quality criteria, regardless of the drug manufacturer country. At the present stage, requirements of medicines manufacturers to the APIas suppliers are extremely high, so enterprises of pharmaceutical substances industrial synthesis have to improve these processes to a higher level, widely applying quality management principles. Herewith, it should consider efficiency, economy and synthetic processes, and also achieve standard results concerning purity quantitative content of the active ingredient, qualify impurities, aim to reduce their formation during production process, and to monitor side processes.

The determining factor of drug quality is the quality of active pharmaceutical ingredients. The Guidelines for their good development and manufacture [2] appeared relatively recently – in 2000. ICH Q7 exactly defines the framework conditions for quality assurance during development and in the process of APIs industrial production.

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In the APIs synthesis in industrial conditions it should be considered both final product quality requirements (which is certainly in priority), and also manufacture safety for personnel and environment [3]. Given this, the Quality by Design concept has a great importance [4,5] in production design (department area) in general, and in production design for every specific API [1,6].

To optimize scientific studies in area of standardization of the substances production under pharmaceutical company conditions, we have analyzed the current requirements in accordance with the Quality by Design concept [7,8]. Literature data analysis points to a lack of systematic universal research devoted to the active pharmaceutical ingredients synthesis standardization [9].

The aim of our research is theoretical foundation and development of the algorithm of active pharmaceutical ingredients industrial synthesis technology standardization in technology transfer or implementation into manufacture based on the Quality by Design concept and Green Chemistry Principles.

Results and Discussion

In the first stage of our research, we have identified the most important requirements (criteria) to form the algorithm of action sequences in the APIs production.

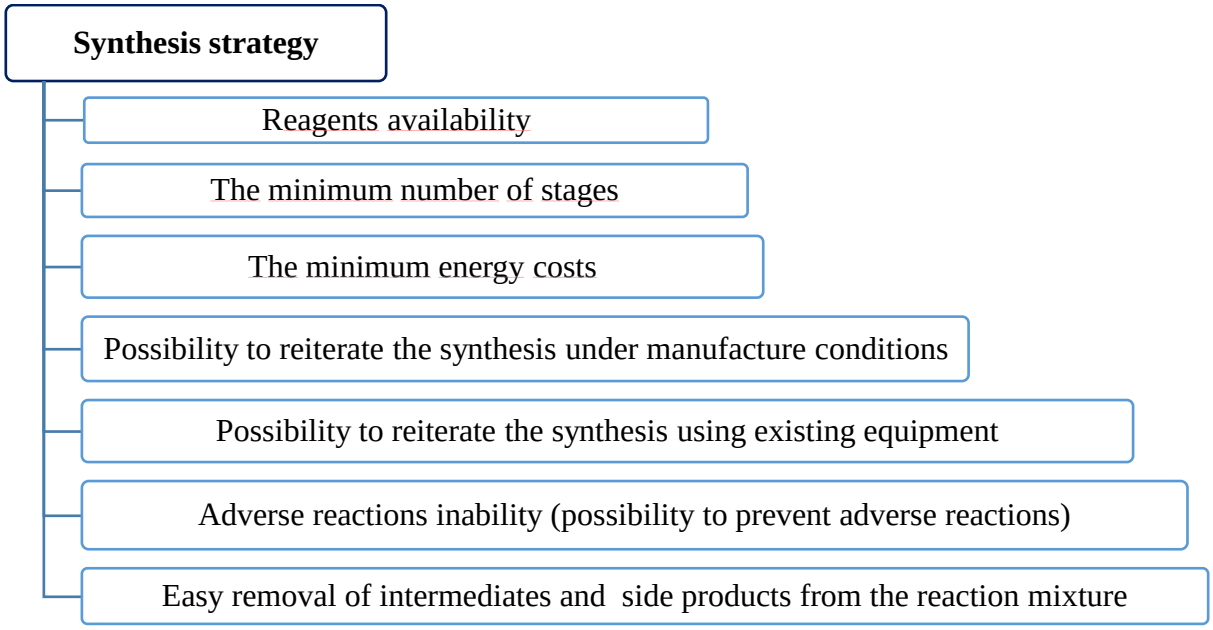
The main criteria in the design/selection/transfer of the substances synthesis technology in terms of the pharmaceutical company are:

- Product's high quality (accordance to the requirements of the State Pharmacopoeia [10,11];
- High product yield;
- Robustness, reproducibility;
- Safety;
- Low environmental effect;
- Profitability.

The next step was to specify the selected criteria regarding the synthesis process and actually the technology.Since APIs influence directly on patient health, therefore, the choice of the method for synthesis which would allow receiving the final product with a minimum number of related impurities [12,13] and, at the same time, providing APIs high yield [14] is crucial for their high quality. To ensure stable APIs purity parameters, the necessary step is to standardize the process of crystallization [15]. In industrial production of APIs the use of solvents with the least possible toxicity indicators [10,16], which also affects the substance general toxicity, is reasonable. Therefore, the number of synthetic steps, crystallization process [17] and the excipients used (Acidifiers, osadzhuvachi etc.) will expectedly effect on the substance purity parameters [18].

To optimize and standardize APIs synthesis design under industrial conditions, we summarized the criteria for the choice of strategy of chemical synthesis of the desired product (FIG. 1).

FIG. 1. **Criteria for the Formation of Design – the Choice of Strategy Synthesis of Chemical Substances (APIs) in Industrial Pharmaceutical Manufacture.**

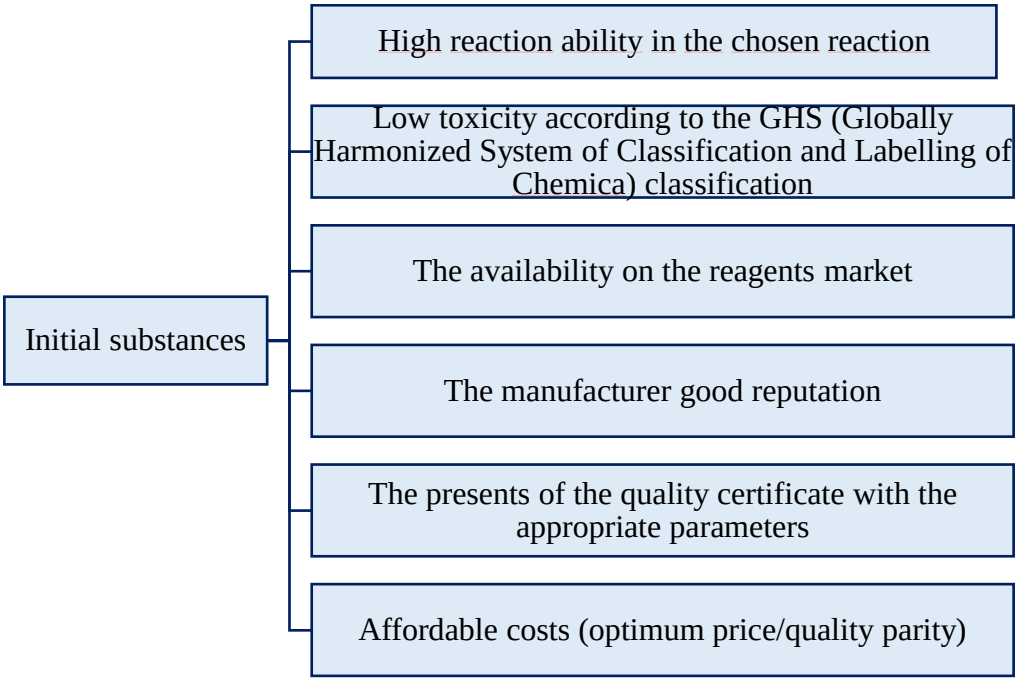


APIs high quality provides obtaining chemical substances in result of synthesis that meet the quality parameters of the current specifications or the SP requirements. Selection and formulation of quality requirements for initial substances are: the choice of initial substances preferred for the synthesis; the assay, the presence of toxic contaminants, manufacturer's quality certificates, and the obtaining method used.

Besides, the proposed value and the manufacturer reputation are also important. However, the latter criteria are strictly within the competence of Supply department and are not included into the purposes of the given study.

Considering Quality by Design and Green Chemistry concept approaches [19,20], we have formulated the criteria for initial substances selection for the further use in the APIs industrial synthesis (FIG. 2).

FIG. 2. **The Criteria for Initial Substances Selection for the Further APIs Industrial Synthesis.**

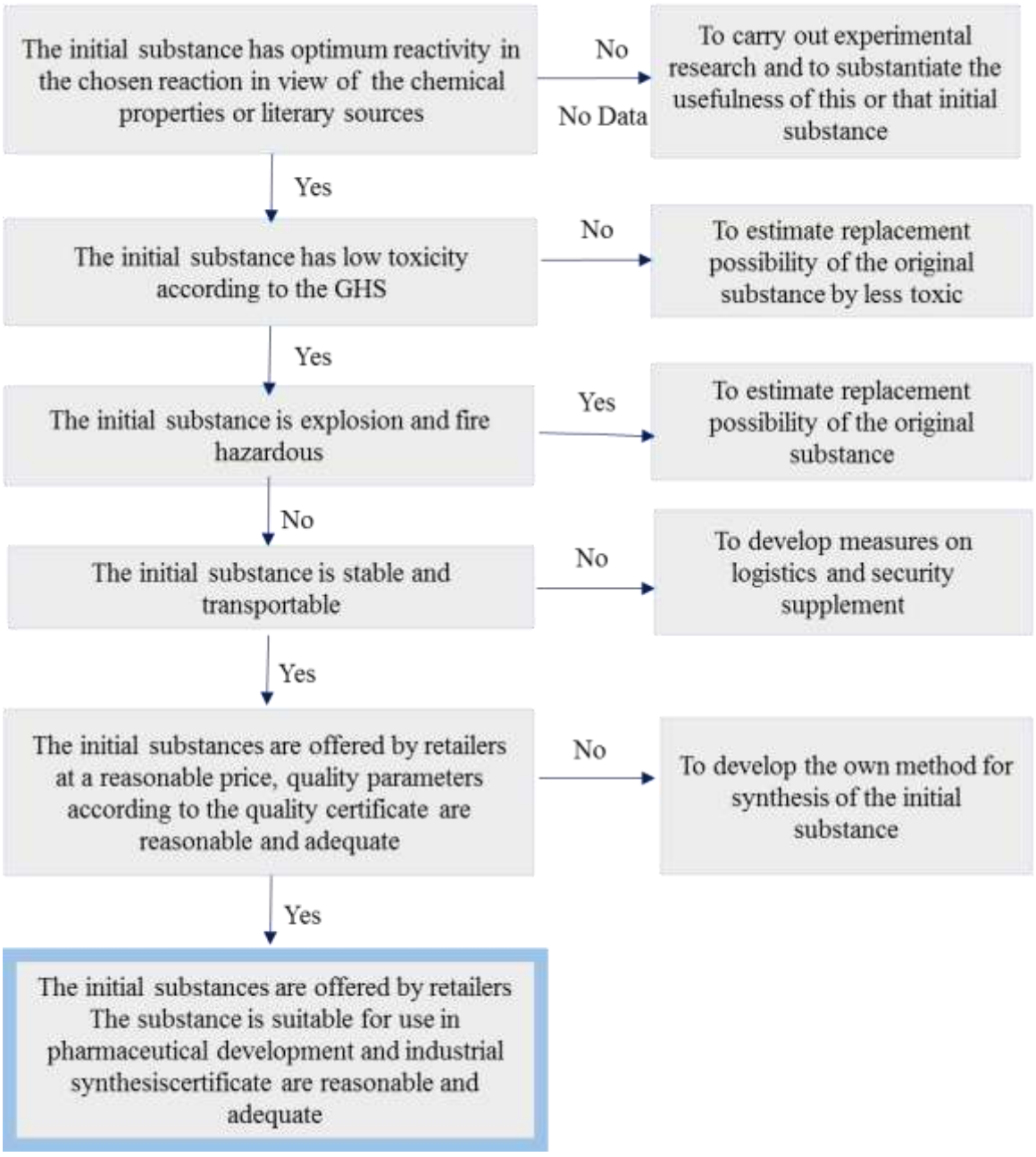


In the system of quality assurance and any enterprise functioning, the result depends on correct decisions. Every process should be standardized and documented. Usually, a "decision tree" creation, typically consisting of scientific data and personal experience review, helps to ensure such systems. Such planning allows both to identify the necessary steps, and to determine the selection criteria and problems solutions in case of any discrepancy of the substances to necessary criteria. We have built a decision tree for reagents selection for use in the APIs industrial synthesis (FIG. 3).

We put to the decision tree the criteria for initial substances that are suitable industrial synthesis of APIs (FIG. 2) according to our opinion and results of the analysis of scientific publications in this area [9,21,22]. Henceforward, we considered measures to be taken if the substance does not meet this or that criteria. As a result, we have identified the steps that need additional studies or when it is necessary to evaluate the necessity and possibility of replacing the proposed initial substances by other. Besides, in some cases it may be necessary to develop and to realize synthesis of the initial substances on their own. It should be taken into account that in addition to chemical and pharmaceutical parameters, economic factors are also important in this process, which along with others will be crucial for supplier choice and in the future – for synthesis strategies.

Of course, the decisions taken during the initial substances selection, have a lot of limitations. It should be considered, that in some cases, the certain substance, even if most of its criteria, more than expected, does not correspond the requirements, can be the only possible in the synthesis or at some stage. In this case all the risks involved should be thoroughly evaluated and the decision about expediency (the need) of the process implementation in the manufacture area or about usability of these key intermediates if they are available on chemical market.

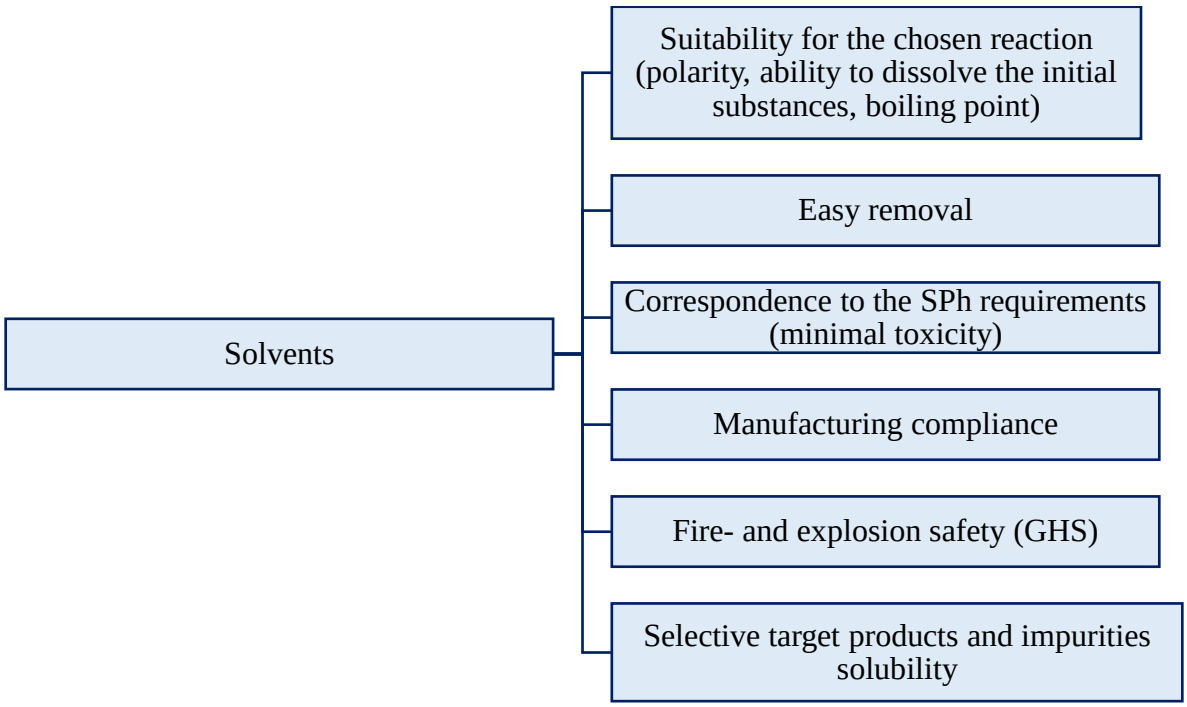
FIG. 3. **A Decision Tree for Reagents Selection for their use in the APIs Industrial Synthesis.**



The choice of solvents in the APIs synthesis is a separate issue. Different researches devoted to the given problem are carried out worldwide. Of course, reactions without are optimum [23,24], as well as reactions in the aquatic environment [16,25] but it is not always possible, suffice it to say it is possible extremely rare. Therefore, the choice of solvents usually requires a large amount of experimental research.

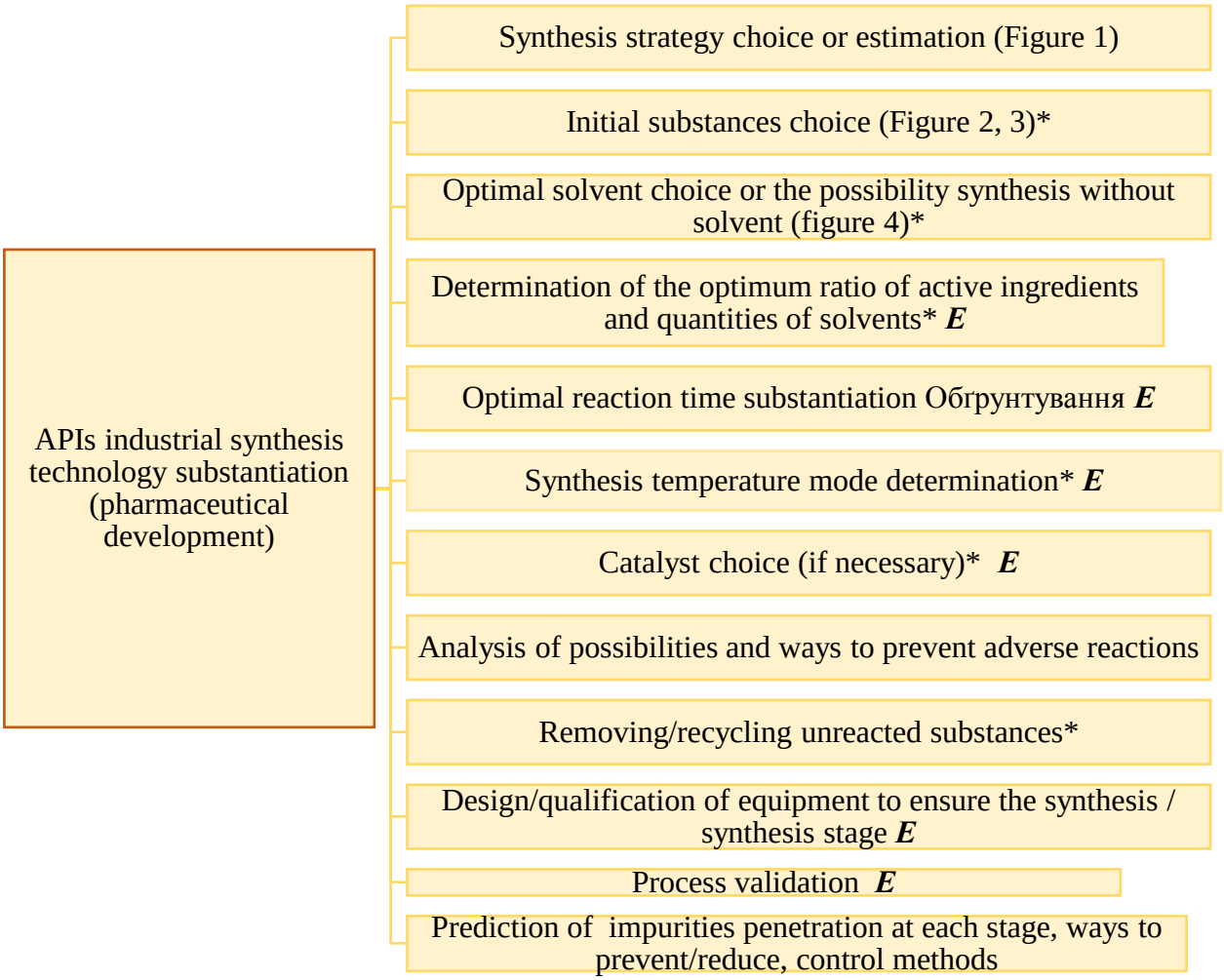
In general, the selection criteria for initial substances and solvents are similar to the criteria for the all chemical industry. Fact that distinguishes this option – is to ensure that products meet the Pharmacopoeial requirements concerning the impurities content and residual amounts of solvents (FIG. 4).

FIG. 4. **The solvents selection criteria for the use in APIs industrial synthesis.**



Besides, it is recommended to avoid in the APIs production the use of solvents of 1-2 hazard classes10, including Acetone, Acetonitrile, Hexane, Dioxane, Toluene, Formamide, Chloroform, Methanol and others. Pharmaceutical development (the synthesis method design and development under laboratory conditions and its transfer to semi industrial and industrial conditions). Pharmaceutical development in the APIs synthesis technology aims to achieve necessary physico-chemical and chemical properties (crystal structure/ polymorphism, solubility) to provide the expected pharmacological effect and possible use in further dosage forms production. Herewith, the proceeding and selection of synthesis strategy, prediction and selection of optimal reaction conditions (time, temperature, catalysts, solvents, etc.) according to the results of experimental studies, quantitative determination and if necessary qualification of impurities, their possible effects on human's body prediction, substantiation of structure and relative purity (UV, IR, NMR spectroscopy, chromatography) of final products and semi products (if any) are rather important [26,27]. To optimize pharmaceutical development concerning APIs synthesis technology, we analyzed the main stages and criteria of this process and formed the algorithm of development/transfer of APIs synthesis technology under manufacture conditions (Scheme 5) and its purification/crystallization (Scheme 6).

FIG. 5. **The Stages of Pharmaceutical Development (Technology Transfer) at APIs Industrial Synthesis.**



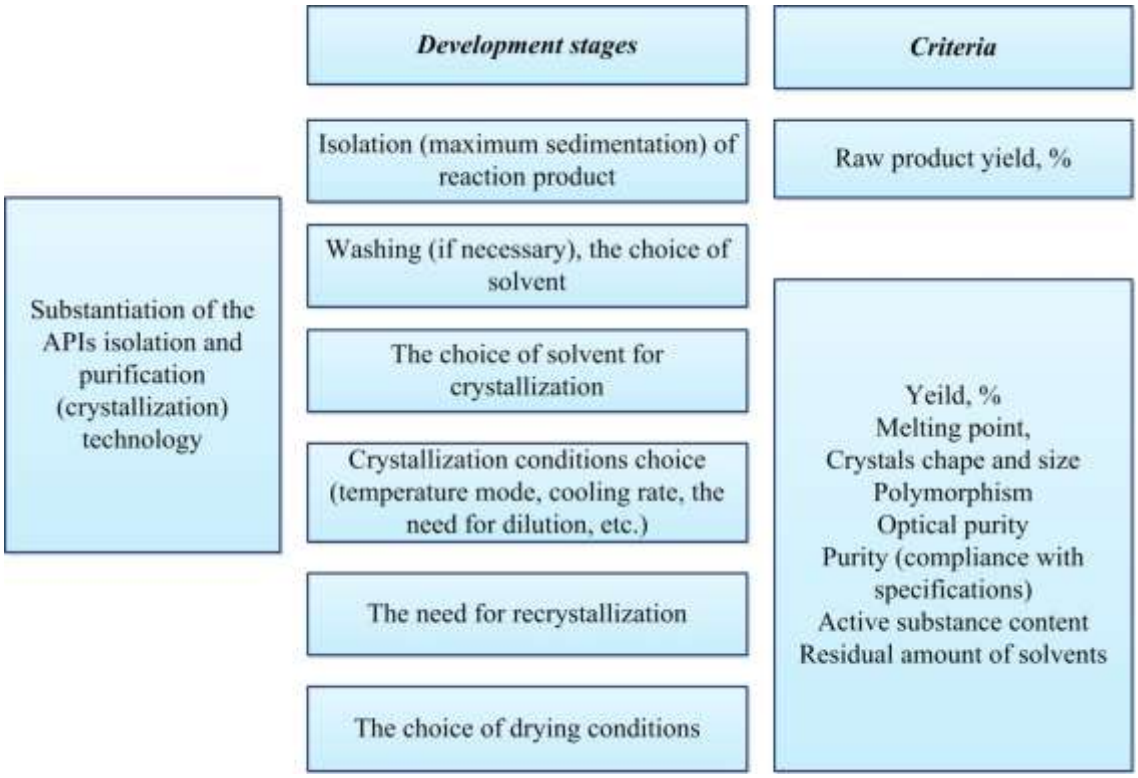
Notes: * – according to the Green Chemistry principles

***E* –** based on the experimental research

To ensure high product yield is important, not only due to production economy. This option is directly related to the safety and quality of synthesized substance. The low product yield (as well as increasing the number of synthesis stages) increases the risk of pollution by unreacted substances, intermediates and side products. To provide high product yield, one of the key factors is the choice both of active ingredients correct ratio, and the solvent nature and amount that ensures the reaction completeness, constant temperature, effective removing of impurities during the purification (crystallization) and precipitation completeness during the substance isolation.

The process and stages of cleaning technology were displayed separately (FIG. 6), because physico-chemical and technological characteristics of APIs (melting point, solubility, size and shape of the crystals, etc.) are formed in result of this stage and its purification happens. In addition, the synthesis final product yield (API) depends on the correctly selected crystallization technology.

FIG. 5. **Stages and Efficiency Criteria for Substantiation of APIs Isolation and Purification Technology under Manufacture Conditions.**



In view of the current requirements, Pharmaceutical companies are headed for the Green Chemistry Principles implementation, therefore during the stage of development and transfer of technology one of the objectives is to achieve maximum compliance of the given technology with these principles, and changes are made if possible (if necessary). As it is shown on the FIG. 5, these principles should be considered in all steps of selection of the initial substances, catalysts (if reasonably necessary) and solvents, technology development (determination of temperature mode and reagents ratio), development of the process of isolation and recycling of substances unreacted during synthesis. Chart of the Green Chemistry Principles transfer under conditions of substances industrial synthesis is presented on FIG. 7 [28].

FIG. 7. **Cause and Effect Diagram of the Green Chemistry Principles use during APIs Industrial Synthesis.**

Green Chemistry Principles [5]	Synthesis (development) steps	Target options
1. It is better to prevent the loss than to clean and recycle the remains	Development of methods: the number stages, substances, side process prevention	The final product purity, yield Amount of waste
2. Synthesis methods are chosen in order to transfer most of the used materials in the product	Development (transfer) of method, the choice of reagents, solvents, catalysts	The total yield after synthesis and purification
3. Reagents and the final product should be the least hazardous to humans and the environment	Initial substances and solvents choice	Hazard class of reagents (GHS) and product (experimental data)
4. New products must be as effective as existing and less toxic	A targeted search of biologically active substances, pharmacological studies	Pharmacological effect and toxicity
5. It's better to not use at all both solvents and separate agents	Development of method for synthesis without solvent	The possibility of the synthesis without solvent
6. Considering energy costs and their influence on environment and the product price	Development of method for synthesis under almost environmental conditions	The possibility to perform the synthesis at normal temperature and pressure
7. Materials should be regenerated in all cases where it is technically and economically profitable	Development of methods for recycling of excess reagents and side products	Maximum product yield obtaining
8. If possible, to avoid obtaining intermediate products (blocking group, deprotection etc.)	Development (transfer) of method for synthesis without intermediate products isolation	Synthesis without intermediate products isolation
9. Always prefer a catalytic process	Development (transfer) of method	Reaction selectivity
10. Chemical product after use should decay to safe substance	Development (transfer) of method for synthesis and recycling of the reagents	The absence of the toxic waste
11. Analytical support for the control of hazardous products formation in real time	The use of process-analytical technology methods	Control of probable hazardous products formation
12. The risk of chemical hazards (explosion, fire, etc.) should be minimal	The choice of initial substances according to their safety (GHS)	Reagents fire- and explosion safety (GHS)

Conclusion

According to the Quality by Design Concept and Good Manufacturing Practice for active pharmaceutical ingredients the algorithms for initial substances and solvents selection, as well as synthesis strategies and technology at the development, scaling or transfer of technology were theoretically substantiated and developed. The main factors, influencing on APIs quality during their industrial synthesis were highlighted. The amount of experimental research necessary for API synthesis technology develop / transfer (chemical reagents and the data about their safety analysis; development and further scaling of the laboratory synthesis method under industrial conditions, including substantiation of the solvents and catalysts choice;

allocation of the critical points and the process validation; development of the quality control methods and process-analytical technology) was determined. The algorithm of the use and eligibility criteria of the given methods to the Green Chemistry Principles for APIs industrial production were summarized and justified.

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