ANNEX

to the Recommendation No. _____ of the
Board of the Eurasian Economic Commission
dated _____, 20___

GUIDELINES
on Pharmaceutical Development of Medicines

I. General Provisions

1. The Pharmaceutical Development Section devoted to the marketing authorization application of a medicinal product enables using the knowledge gained from applied scientific approaches and quality risk management to developing a medicinal product and its manufacturing process. The Section is a part of the marketing authorization application of a medicinal product submitted for registration and is subsequently updated by the marketing authorization holder based on the new data and information obtained during the medicinal product's life cycle. The Pharmaceutical Development Section allows experts from authorized authorities (expert organizations) and pharmaceutical inspectors to provide the comprehensive understanding of medicinal product characteristics and manufacturing process. Besides, the Guidelines describe the areas where the provision of profound pharmacy and scientific information on medicinal product manufacture may lay the basis for the authorized authorities (expert organizations) to apply some flexible regulatory approaches. The extent to which the decisions made by the authorized authorities are flexible depends on the level of scientific knowledge provided.

2. These Guidelines describe the quality by design (QbD) principles and are not intended to establish any new standards or impose new requirements. It shows

how an applicant may practically apply some concepts and tools (e.g., a design space) to different dosage forms. If a pharmaceutical company decides to apply quality by design and quality risk management established in Part III of the Good Manufacturing Practice of the Eurasian Economic Union (GMP) approved by Decision No. 77 of the Council of the Eurasian Economic Commission dated November 3, 2016 (hereinafter, the Good Manufacturing Practice), it obtains some additional possibilities of extending its scientific and risk-based approaches to managing quality of a medicinal product.

II. Scope

3. These Guidelines provide instructions on compiling Section 3.2.P.2, Pharmaceutical Development, of the marketing authorization application for medicinal products in the Common Technical Document (CTD) format. The Guidelines do not apply to marketing authorization applications for medicinal products being in clinical development. However, these Guidelines may be also taken into account at the clinical development stages. This Guidelines may also be applicable to some other types of medicinal products. The applicants may consult the appropriate authorized authorities to determine whether these Guidelines are applied to a particular type of medicinal products.

III. Definitions

4. For the purposes of these Guidelines, the terms below shall have the following meaning:

“real-time release” shall mean the ability to assess and deliver quality of intermediates and/or medicinal products based on process data that includes a reliable combination of measured characteristics of a medicinal product and types of in-process control;

“proven acceptable range” shall mean the characterized range of a process parameter, operation within which (with all other parameters unchanged) will result in a material that meets the relevant quality criteria;

“life cycle” shall mean all phases of medicinal product development and circulation, starting from its initial development, throughout its time on the market, and up to its withdrawal from the market;

“quality of the medicine” shall mean the suitability of an active pharmaceutical ingredient or medicinal product for its intended use, including by such attributes as identification, dosage, and purity;

“experiment planning (experiment design)” shall mean a structured, organized method to determine the dependence between factors affecting the process being studied in the experiment and the result of such experiment;

“quality by design (QbD)” shall mean a systematic approach to medicinal product development based on trustworthy scientific rationale and quality risk management that starts with the goals previously set to emphasize the understanding of the intended use of the medicinal product and process, as well as its in-process control;

“design space” shall mean a multidimensional combination and interaction of input variables (e.g., material characteristics) and process parameters that has proven its ability to deliver quality of the product;

“process analytical technology (PAT)” shall mean a system of designing, analyzing, and controlling the manufacturing process by means of timely measurements (i.e., during processing) of critical quality attributes and functional characteristics of the raw and in-process materials being processed or technological processes in order to deliver quality of the product (including medicinal product);

“process robustness (stability)” shall mean the ability of technological process to withstand variability of materials and changes in the process or equipment without any adverse effect on quality of the product (including medicinal product);

“control strategy” shall mean a planned set of control tools known at this stage that is based on the characteristics and properties of a medicinal product and technological process. Such set of tools ensures the proper implementation of such technological process and quality of the medicinal product;

“target quality profile of a medicinal product (TQPP)” shall mean a planned set of quality attributes for a medicinal product that will, at its best, be achieved to ensure the desired quality, taking into account the medicinal product safety and efficacy.

The terms “critical quality attribute”, “critical process parameter” and “continuous process verification” used in these Guidelines shall be used in the meanings defined in the Good Manufacturing Practice.

IV. Pharmaceutical Development

5. Pharmaceutical development is aimed at creating a high-quality medicinal product and its manufacturing process in order to consistently create the planned functional characteristics of the medicinal product. Information and knowledge obtained from the pharmaceutical development studies and manufacturing experience allow us to gain scientific understanding in order to provide rationale for the established design space, specifications, and manufacturing process control.

6. Information from pharmaceutical development studies may form the basis for quality risk management. Since it is impossible to guarantee quality of the medicinal product only by testing such medicinal product, its quality is built into the medicinal product when designing it. Changes in formulation (batch formula) and manufacturing processes while developing and managing the medicinal product’s life cycle should be considered as possibilities of gaining additional knowledge and providing further rationale for the design space creation. It is also expedient to include relevant data from experiments that have yielded unexpected results. The design space is proposed by the applicant as part of the marketing authorization application and is subject to expert assessment when registering the

medicinal product or making amendments to its marketing authorization application.

The pharmaceutical manufacturer’s operation within the design space shall not be considered an amendment to the marketing authorization application. Going outside the design space shall be considered a change and shall entail the process of making amendments to the marketing authorization application of the medicinal product.

7. The Pharmaceutical Development Section includes information confirming that the selected type of dosage form and the proposed formulation and technology are suitable for the intended use of the medicinal product. This Section should include information in each part, which is necessary to properly represent the development of medicinal product and process, as well as summarized tables and charts (if they enhance understanding and facilitate assessment).

8. At the very least, it is necessary to identify the aspects of pharmaceutical ingredients, excipients, packaging (closure) systems, and manufacturing processes, which are critical to quality of the medicinal product, and provide rationale for the control strategies. Critical formulation and process attributes are typically identified by assessing the extent to which their variability may affect quality of the medicinal product.

9. The applicant shall be entitled to conduct some pharmaceutical development studies which may provide greater information on the functional characteristics of the medicinal product in a wider range of material quality attributes, processing options, and process parameters. If such additional information is included in this Section, greater understanding of material characteristics, processes, and their control may be demonstrated. Such scientific understanding facilitates the establishment of an expanded design space. In such situations, there are possibilities for developing more flexible approaches to regulating the circulation of medicinal products, for example, to facilitate:

risk-based decisions of authorized authorities (expert organizations) of the Eurasian Economic Union Member States (hereinafter, the Member States, the Union);

improvement of the manufacturing process within the approved design space described in the marketing authorization application without assessing by the Member State's authorized authority (expert organization) when making amendments to the marketing authorization application;

reduction in requests for making amendments to the marketing authorization application of a medicinal product;

implementation of in-process quality control in real time to reduce the release control tests of final product (including the medicinal product).

10. The applicant should provide more extensive information on the functional characteristics of the medicinal product in the range of material quality attributes, process capabilities, and process parameters. Such information may be obtained using, for example, experiment planning, process analytical technology (PAT) and/or preliminary knowledge. Appropriate use of quality risk management principles may be helpful in making decisions about whether additional pharmaceutical development studies are necessary to gain such knowledge.

11. The pharmaceutical development studies shall be planned and implemented based on the planned scientific objective. The level of knowledge obtained (rather than the data volume) shall be the basis for forming some science-based information included in the materials of the marketing authorization application and its subsequent assessment by the Member State's authorized authority (expert organization).

1. Medicinal Product Components

Active Pharmaceutical Ingredient

12. For the active pharmaceutical ingredient, the following aspects shall be identified and studied:

а) physicochemical and biological properties of the active pharmaceutical ingredient that may affect functional characteristics of the medicinal product;

б) suitability of the active pharmaceutical ingredient for the technological process;

в) properties that have been purposefully incorporated into the active pharmaceutical ingredient (e.g., properties of pharmaceutical solids).

13. Examples of physicochemical and biological properties, which may require studying, include solubility, water content, particle size, crystal properties, biological potency, and permeability.

14. The properties specified in subclauses 12 (a) to (c) may be interrelated and should be considered in a body.

15. To assess the potential effect produced on a medicinal product behavior by physicochemical properties of the active pharmaceutical ingredient, medicinal product studies should be performed. Circumstances under which medicinal product studies should be performed are described in Annex No. 1 to the Guidelines for Preparing a Normative Document on the Medicinal Product Quality approved by Decision No. 151 of the Eurasian Economic Commission's Board dated September 7, 2018 (hereinafter, respectively, the Guidelines for the Normative Document) (e.g., decision trees No. 6 and No. 7). The same circumstances may be applied to design quality and develop specifications of biological medicinal products stipulated in Chapter 6 of the Rules for Conducting Studies of Biological Medicinal Products of the Eurasian Economic Union approved by Decision No. 89 of the Council of the Commission dated November 3, 2016 (hereinafter, the Rules for Studies of Biological Medicinal Products.) The results of studies on the potential effect produced by properties of the active pharmaceutical ingredient on functional characteristics of the medicinal product may be used (based on the circumstances) to provide rationale for the active pharmaceutical ingredient's specification in Section 3.2.S.4.5 of the marketing authorization application.

16. The compatibility of active pharmaceutical ingredient with the excipients listed in section 3.2.P.1 of the marketing authorization application should be assessed. For medicinal products containing more than one active pharmaceutical ingredient, their compatibility with each other should also be assessed.

Excipients

17. Consideration should be given to the excipients chosen, their content (concentration), and characteristics that may affect the functional performance (e.g. stability, bioavailability) or process suitability of the medicinal product in terms of the respective function of each excipient. This applies to all substances used in the medicinal product manufacture, regardless of whether they enter the medicinal product (e.g., processing additives). Compatibility of excipients with other excipients should be established where it is important (e.g., combining a dual preservative system). The capability of excipients (e.g., antioxidants, permeation enhancers, disintegrators, release control agents) to provide the intended functionality and maintain it throughout the planned shelf life (expiration date) of the medicinal product should also be proven. If necessary, information on functional characteristics of excipients should be used to provide rationale for the choice of excipient and its quality attributes, as well as rationale for the medicinal product’s specification in Section 3.2.P.5.6 of the marketing authorization application of the medicinal product.

18. Reference should be made to the information which provides rationale for the excipient safety in Section 3.2.P.4.6 of the marketing authorization application (if applicable).

2. Medicinal Product

Dosage Form Development

19. A summary shall be provided to describe the formulation development and point out those attributes which are critical to quality of the medicinal product,

taking into account its planned use and route of administration. For identifying some critical or interacting variables that are potentially significant for delivering quality of the medicinal product, information obtained while planning the experiment should be used.

20. The summary should describe the process of changing the formulation, dosage form, and pack size (medicinal product design), from the initial version to the final formulation, as well as provide rationale for choosing the medicinal product components (e.g. properties of the active pharmaceutical ingredient, excipients, packaging (container closure) system, and any relevant dosing device), the manufacturing process and, where necessary, information obtained while developing a similar medicinal product.

21. Any ranges of excipient content included in the batch formula should be substantiated. This rationale may be based on experience gained while developing or manufacturing the medicinal product.

22. The summary of formulations used in clinical safety and efficiency studies and any relevant bioavailability or bioequivalence studies should be provided. Any changes between the batch(es) of the medicinal product proposed for manufacture and those manufactured and used in the reference clinical studies, as well as the primary batch manufactured for stability studies, should be described in detail and the rationale for such changes should be provided.

23. It is necessary to generalize the information from comparative studies *in vitro* (e.g., comparative dissolution kinetics test) or comparative *in vivo* studies (e.g., bioequivalence study), which link the formulation and dosage form of the medicinal product batches used for clinical trials to the proposed formulation and dosage form of the medicinal products intended for the industrial manufacture described in Section 3.2.P.1 of the marketing authorization application, and provide cross-references to such studies (with study numbers specified).

If any attempts have been made to establish an *in vitro – in vivo* correlation, the results of such studies and cross-references thereto (with study numbers specified) should be provided in the specified section of the marketing

authorization application. Successful correlation may facilitate the choice of appropriate acceptance criteria for the dissolution test and may potentially reduce the need for further bioequivalence studies after any significant changes to the medicinal product (e.g., formulation, dosage form, physical characteristics of the dosage form, etc.) or its manufacturing process.

24. Any specific design features of the medicinal product (e.g., availability of a score line on tablet, excess weight or filling volume of dosage unit of the medicinal product, measures against counterfeiting, if such design features affect the medicinal product) should be noted and the rationale for their use should be provided.

Overages

25. It is not recommended to use any overages of the active pharmaceutical ingredient to compensate for its degradation during the manufacturing process or shelf life of the medicinal product or to extend its shelf life (expiration date).

26. For any overages in the medicinal product manufacture, whether they are included into the final formulation or not, rationale should be provided based on the medicinal product safety and efficacy. Information should be provided regarding:

the quantity of overages;

the causes for the overages (e.g., creating overages to compensate for expected and documented losses in manufacture);

the rationale for the quantity of overages.

The overages should be included into the assay specified in the batch formula (into Section 3.2.P.3.2 of the marketing authorization application).

Physicochemical and Biological Properties

27. Physicochemical and biological properties affecting the safety, functional characteristics or process suitability of the medicinal product should be

noted and considered. The said properties include the relations of quality attributes of the active ingredient and dosage form with their biological effect. The studies may include, e.g., developing a respirable fraction test for an orally inhaled medicinal product. Section 3.2.P.2.2.3 of the marketing authorization application may provide information serving as a rationale for the choice between a dissolution test or disintegration test or other means of ensuring the active substance release or design and suitability of the chosen test, subject to Annex No. 1 of Guidelines for the Normative Document (decision tree No. 7 (part 3) and decision tree No. 3 (part 1)) and Chapter 6 of the Rules of Biological Medicinal Products Research. The rationale for the medicinal product development should provide references to any relevant data from the stability studies included in Section 3.2.P.8.3 of the marketing authorization application.

3. Manufacturing Process Development

28. Rationale should be provided for any choice, control system, and improvements to the manufacturing process described in Section 3.2.P.3.3 of the marketing authorization application (i.e. intended for industrial batches). Critical attributes should be considered along with available manufacturing process options to explain the process choice and prove the expediency of components. The suitability of the equipment used for the planned medicinal products should be described. Process development studies should provide the basis for manufacturing process improvement, validation of such process, continuous verification of the manufacturing process (if applicable), and any requirements for the manufacturing process control. Where appropriate, such studies should include microbiological and physical and chemical attributes. Information obtained from the process development studies may be used (if necessary) to provide rationale for the medicinal product’s specification in Section 3.2.P.5.6 of the marketing authorization application.

29. The manufacturing process development program or manufacturing process improvement program should identify any critical process parameters that require monitoring or control (e.g., granulation endpoint) to deliver the desired quality of the medicinal product.

30. For medicinal products that must be sterile, a suitable method for sterilizing the medicinal product and primary packaging material should be chosen and the rationale for such choice should be provided.

31. Significant differences between the manufacturing processes used to manufacture some batches for pivotal clinical trials (safety, efficiency, bioavailability, bioequivalence) or primary stability studies and the manufacturing process described in Section 3.2.P.3.3 of the marketing authorization application should be described and analyzed. The analysis should summarize the effect of differences on functional characteristics, manufacturability, and quality. The information should be provided in the way that facilitates comparison of manufacturing processes and relevant data obtained from the batch analyses (Section 3.2.P.5.4). Such information includes, e.g., the following:

identification (e.g., batch number) and the intended use of the batches manufactured (e.g., batch number for a bioequivalence study);

name of the manufacturing site;

batch size;

any significant differences in equipment (e.g., different design, operating principle, size).

32. To provide flexibility for future process improvement, when describing the manufacturing process development, it is necessary to describe measurement systems that allow monitoring of critical attributes or endpoints of the manufacturing process. Collecting process monitoring data during the manufacturing process development may provide useful information to better understand the process. Manufacturing process control strategies should be described that enable adjustments to the manufacturing process to ensure that all critical attributes are under control.

33. It is acceptable to provide assessment of the ability of the manufacturing process to reliably manufacture the medicinal product with the planned quality (e.g., the manufacturing process operation under different working conditions, at different scales, or with different equipment). Understanding the robustness (stability) of the manufacturing process may be useful to assess and mitigate the risk and provide rationale for future manufacturing and process improvements, especially when combined with the aid of risk management tools in accordance with Chapter 2, Part III of the Good Manufacturing Practice.

4. Packaging (Container Closure) System

34. The choice and rationale for choosing a packaging (container closure) system for the industrial batch of the medicinal product (described in Section 3.2.P.7 of the marketing authorization application) should be described. Consideration should be given to the planned use of the medicinal product and the suitability of the packaging (container closure) system for its storage and transportation (shipment), including assessment of packaging for bulk medicinal products (where applicable).

35. The rationale for the choice of primary packaging materials should be provided, including the description of studies performed to confirm the container and closure integrity. Consideration should be given to possible interactions between the medicinal product and the container or its marking.

36. When choosing the primary packaging, one should consider, e.g., the choice of packaging materials, protection from moisture and light, compatibility of the structural materials with the dosage form (including sorption by the container and leaching), and safety of the structural materials. Where appropriate, rationale for the choice of secondary packaging materials should be provided in accordance with the requirements.

37. If a dosing device (e.g., dropper pipette, pre-filled syringe, inhaler) is used, reproducible and accurate delivery of the medicinal product dose should be

demonstrated under test conditions that simulate as closely as possible the administration of the medicinal product.

5. Microbiological Characteristics

38. If justified, Section 3.2.P.2.5 of the marketing authorization application should describe microbiological attributes of the medicinal product. Such description includes, e.g., the following:

the rationale for conducting or not conducting any microbial limit tests for non-sterile medicinal products (e.g., decision tree No. 2 of Annex No. 1 of Guidelines for the Normative Document and Chapter 6 of the Rules of Biological Medicinal Products Research);

the selection and efficacy of preservative systems in medicinal products containing an antimicrobial preservative, or the antimicrobial efficacy of medicinal products that themselves have antimicrobial effects;

for sterile medicinal products, the integrity of the packaging (container closure) system as it affects the prevention of microbial contamination.

39. Despite the fact that a chemical test for preservative content is an attribute included in the medicinal product specification, the efficacy of an antimicrobial preservative should be proven during development. During the antimicrobial preservative efficiency test, it should be proven that the lowest established concentration of antimicrobial preservative is effective for microbial content control. The concentration used should be justified in terms of efficacy and safety to ensure that the concentration of preservative is used at a bare minimum that provides the required efficiency level throughout the planned shelf life (expiration date) of the medicinal product. If expedient, during development, a microbiological challenge test should be performed under test conditions, which simulate use by a patient as closely as possible, and provide its results in Section 3.2.P.2.5 of the marketing authorization application.

6. Compatibility

40. To provide the rationale for any necessary and proving information about the medicinal product, information about the medicinal product compatibility with liquids for recovery (e.g., precipitation, stability) should be studied and included in Section 3.2.P.2.6 of the marketing authorization application. Such information should cover the recommended shelf life (expiration date) of the ready-to-use medicinal product at the recommended storage temperature and at the likely concentration extremes. It may also be necessary to study mixing or dilutions of medicinal products before their administration (e.g., adding a medicinal product to large volume infusion containers).

IV. Approaches to Pharmaceutical Development

41. In all cases, the medicinal product should be designed to meet the needs of patients and to ensure that the medicinal product meets its intended functional characteristics. Medicinal product development strategies vary from company to company and for different medicinal products. The approach to development and its scope may also vary and should be included in the marketing authorization application materials. The applicant may choose an empirical approach or more systematic approach to medicinal product development or a combination of both. Annex No. 1 illustrates some possible differences between the said approaches. A more systematic approach to development (also defined as quality by design) may include, e.g., the use of prior knowledge, study results with the aid of experimental design, the use of risk management for quality, and the use of knowledge management throughout the medicinal product’s life cycle. Such a systematic approach may contribute to obtaining the desired quality of the medicinal product and helps the experts of the authorized authority (expert organizations) to better understand the strategy of pharmaceutical development implemented by the company. Understanding the characteristics of the medicinal product and the

manufacturing process may deepen as far as the information gained during the medicinal product's life cycle accumulates.

42. Profound understanding of the medicinal product properties and its manufacturing process may provide the basis for more flexible approaches to regulating circulation of such medicines. The flexibility degree of decisions taken by the authorized authorities is based on the level of relevant scientific knowledge provided in the marketing authorization application. The basis for scientific and risk-based assessments of the marketing authorization application and assessments performed by the authorized authority (expert organization) is the information obtained and provided to the authorized authority (expert organization) rather than the volume of such collected information. Relevant data should be provided in each marketing authorization application to prove that this knowledge is based on trustworthy scientific principles.

43. The pharmaceutical development includes at least the following elements:

formulating a target quality profile of the medicinal product (TQPP) as it relates to quality, safety, and efficiency based on such factors as route of administration, dosage form, bioavailability, dosage, and stability;

identifying potential critical quality attributes (CQA) of the medicinal product so that those characteristics of the medicinal product that affect its quality may be studied and controlled;

determining critical quality attributes of the active pharmaceutical ingredient, excipients, etc., and choice of the type and quantity of excipients to obtain a medicinal product of the desired quality;

choosing the suitable manufacturing process;

drafting a control strategy.

44. A profound quality-by-design approach to medicinal product development additionally includes the following elements:

a) systematical assessment, understanding and improvement of formulation and manufacturing process, including:

identification of material characteristics and process parameters that may affect critical quality attributes of the medicinal product (e.g., using prior knowledge, experimentation, and risk assessment);

determination of functional dependencies which link material characteristics and process parameters with critical quality attributes of the medicinal product;

b) use of enhanced understanding of the medicinal product characteristics and manufacturing process along with quality risk management to establish an appropriate control strategy, which may, e.g., include proposed design space(s) and/or real-time release tests.

45. A greater systematic approach promotes continuous improvement and innovation during the medicinal product's life cycle.

V. Elements of Pharmaceutical Development

46. Possible approaches described in this Section to obtain more systematic and enhanced understanding of characteristics of the medicinal product being developed and its manufacturing process, as well as the examples provided, are only for illustration purposes and not intended to create new requirements for regulating circulation of medicines.

1. Target Quality Profile of the Medicinal Product

47. A target quality profile of the medicinal product is a basis for planning the medicinal product development. Factors of the target quality profile of the medicinal product may include the following:

planned use of the medicinal product in the clinical setting, route of administration, dosage form, delivery systems;

dosage(s);

packaging (container closure) system;

the release or delivery of the active ingredient and attributes affecting the pharmacokinetic characteristics (e.g., dissolution, aerodynamic properties) relevant to dosage form of the medicinal product being developed;

relevant quality criteria of the medicinal product (e.g., sterility, purity, stability, release of active ingredient) for the medicinal product planned to be marketed.

2. Critical Quality Attributes

48. Critical quality attributes are as a rule associated with the active pharmaceutical ingredient, excipients, intermediates (in-process materials), and the medicinal product.

49. Critical quality attributes of solid dosage forms for oral administration are those that affect purity, dosage, release of active ingredient, and stability. Critical quality attributes for other delivery systems may additionally include such more drug-specific aspects as aerodynamic properties of inhaled medicinal products, sterility of parenterals, and adhesion properties of transdermal patches. For starting materials and intermediates, critical quality attributes may additionally include those properties that affect critical quality attributes of the medicinal product (e.g., particle size distribution (grain-size distribution), bulk density).

50. Potential critical quality attributes of the medicinal product derived from the target quality profile of the medicinal product and/or previously obtained information are used as guidance for developing a medicinal product and its manufacturing process. The list of potential critical quality attributes may be modified after choosing a formulation and manufacturing process and as far as the information about the medicinal product is accumulated and the manufacturing process is understood. Quality risk management may be used to prioritize a list of potential critical quality attributes for further assessment. Relevant critical quality attributes may be identified through an iterative process of quality risk

management and experimental studies that assesses the extent to which their variability may affect quality of the medicinal product.

3. Risk Assessment: Linking Material Characteristics and Process Parameters to Critical Quality Attributes of the Medicinal Product

51. Risk assessment is a scientific method used in quality risk management (in accordance with Part III of the Good Manufacturing Practice) that may help identify which material characteristics and process parameters potentially affect critical quality attributes of the medicinal product. Risk assessment is as a rule performed at the early stage of the pharmaceutical development process and repeated as far as the amount of information increases and more information about the medicinal product becomes available.

52. Risk assessment tools may be used to identify and rank the parameters (e.g., parameters of process, equipment, starting materials) that have some potential to affect quality of the medicinal product, based on prior knowledge and initial experimental data. An illustrative example is provided in Annex No. 2. An initial list of potential parameters may be quite long, but subject to modification and prioritization during further studies (e.g., through combining the experimental design, mechanistic models). The list may be refined based on experimental results to determine the significance of individual parameters and potential interactions. Once significant parameters are identified, they should be studied in more detail (e.g., through combining the experimental design, mathematical models, or studies leading to a mechanistic understanding of critical quality attributes) to achieve a higher level of manufacturing process understanding.

4. Design Space

53. Dependence between input factors of the manufacturing process (material characteristics and production process parameters) and critical quality attributes is described in a design space (examples in Annex No. 2). Operation within the design space is not considered a change. Going beyond the design space

is considered a change and, as a rule, brings about a post-registration amendment procedure. The design space is proposed by the applicant and is subject to assessment by the authorized authority (expert organization) and subsequent approval during registration or other procedures related to registration.

54. The risk assessment and experimentation during manufacturing process development described in subsection 3 of this Section provide an understanding of the links and impact of manufacturing process parameters and material attributes on critical quality attributes of the medicinal product and help identify variables and their ranges within which quality consistency may be achieved. These process parameters and material attributes should be included in the design space.

55. The marketing authorization application should provide a description of the process parameters and material characteristics considered for the design space and their impact on quality of the medicinal product. The rationale for their inclusion in the design space should be provided. In some cases, the rationale for exclusion of particular parameters should also be provided. Information obtained in studies should be included in the marketing authorization application. Process parameters and material characteristics that have not varied throughout the development should be specified.

Design Space Description in the Marketing Authorization Application

56. The design space should be described in terms of ranges of material characteristics and process parameters or using more complex mathematical dependencies. The design space is described as a time-dependent function (e.g., temperature and pressure cycle within a lyophilization cycle) or as a combination of variables, e.g., components of a multidimensional (multifactorial, multivariate) model. It is also acceptable to include some scaling factors if the design space is intended to cover several operational scales. A retrospective data analysis should be considered when establishing the design space. Regardless of how the design

space is developed, it is expected that operation within the design space will result in the medicinal product that meets the specified quality.

57. Examples of different potential approaches to presenting the design space are provided in Annex No. 2.

Design Space(s) for a Single Operation

58. The applicant may decide to establish some independent design spaces for one or more single operations or a single design space covering multiple operations. Despite the fact that an individual design space for each single operation is often easier to develop, a design space covering the entire process may provide greater operational flexibility. For example, for a medicinal product undergoing degradation in solution before lyophilization, the design space for controlling the degree of degradation (e.g., concentration, time, temperature) may be expressed for each single operation or the sum of all single operations.

Dependence of the Design Space on the Scale of Manufacturing and Equipment

59. When describing the design space, the applicant should consider the type of operational flexibility desired. The design space may be developed at any scale. The applicant should provide rationale for feasibility of applying the design space developed for small and pilot scale to the manufacturing process with the proposed scale of manufacturing and describe and analyze potential risks of the scaling up.

60. If the applicant proposes a single design space applicable to multiple operational scales, the design space should be described in terms of relevant scale-independent parameters. For example, if a mixing operation shows that the medicinal product is shear-sensitive, the design space may include a shear rate rather than a mixing rate. The design space description may include some unit-less figures and/or scaling models.

Design Space and Proven Acceptable Ranges

61. A combination of proven acceptable ranges does not form the design space. However, proven acceptable ranges based on one-dimensional experimentation may provide useful information about the manufacturing process.

Design Space and Failure Boundary

62. A failure boundary should be determined for process parameters or material characteristics beyond which the relevant quality attributes may not be achieved. However, determining a failure boundary or demonstrating failure modes is not mandatory components of establishing a design space.

5. Control Strategy

63. A control strategy is formed to ensure that the medicinal product of specified quality is produced consistently and includes, inter alia, some control tools. Control tools may include parameters and attributes related to materials and components of the medicinal product, facility and equipment operating conditions, types of in-process control, specifications for finished medicinal products, and related monitoring and control methods and frequency. The control strategy elements included in Section 3.2.P.2 of the marketing authorization application should describe and provide rationale for the affect produced on quality of the manufactured medicinal product by in-process controls and control tools for starting materials (active pharmaceutical ingredient and excipients), intermediates (in-process materials), packaging (container closure) system, and medicinal products. These types of control are based on knowledge of the medicinal product characteristics, its formulation and manufacturing process, and at least include control of critical parameters of the manufacturing process and characteristics of starting and other materials.

64. A comprehensive approach to pharmaceutical development will facilitate understanding of the manufacturing process and medicinal product characteristics

and identify some variability sources. Variability sources, which may affect quality of the medicinal product, should be identified, correctly interpreted, and subsequently controlled. Understanding the variability sources and their impact on further processes or processing, in-process materials, and quality of the medicinal product may provide opportunity for shifting types of control to previous stages and minimizing the need for testing at medicinal product release. Understanding the variability sources and their impact on the medicinal product and its manufacturing process along with the quality risk management (in accordance with Part III of the Good Manufacturing Practice) will provide rationale for controlling the manufacturing process in such a way that variability (e.g., of raw materials) may be compensated for by adapting the regime to manufacturing a medicinal product of consistent quality.

65. Such understanding of the manufacturing process may provide a possibility for an alternative manufacturing paradigm with less tightly constraint on variability of starting and other materials. Instead, it may be possible to plan an adaptive stage of the manufacturing process (a stage that responds to the starting materials) with appropriate control of the manufacturing process to deliver consistent quality of the medicinal product.

66. Enhanced understanding of functional characteristics of the medicinal product may provide rationale for using some alternative approaches to determine that the starting and other materials meet their quality attributes. The use of such alternatives may provide rationale for real-time tests. For example, the Dissolution Test may provide indirect evidence of dissolution for rapidly dissolving solid dosage forms with well-soluble active pharmaceutical ingredients. In-process dosage unit uniformity test (e.g., using uniformity of mass along with the near-infrared (NIR) analysis) may enable real-time testing and allow for an increased level of quality assurance compared to traditional release test using pharmacopoeial approaches. Real-time test may replace final product test but does not replace the validation and quality control phases stipulated by the Good Manufacturing Practice for batch release.

67. The control strategy may include, inter alia, the following:

control of starting material characteristics (e.g., active pharmaceutical ingredient, excipients, primary packaging materials) based on understanding of the effect they produce on manufacturing process or quality of the medicinal product;

specification(s) of the medicinal product;

control of single operations that affect further processing or quality of the medicinal product (e.g., effect of drying on degradation, particle size distribution of the granulate on dissolution);

in-process or real-time tests instead of final product tests (e.g., measuring and control of critical quality attributes throughout processing);

monitoring program (e.g., regular integrated analysis of the medicinal product) to verify predictive multifactorial models.

68. The control strategy may include different elements. For example, one element of the control strategy may be based on final product test, while another may depend on the real-time test. Any marketing authorization application should describe the rationale for using such alternative approaches.

69. These Guidelines should be applied to provide rationale for alternative approaches to establishing attributes and specification acceptance criteria as described in Annex No. 1 of Guidelines for the Normative Document and Chapter 6 of the Rules of Biological Medicinal Products Research.

6. Life Cycle Management and Continuous Improvement

70. Throughout the medicinal product’s life cycle, companies have possibilities to assess innovative approaches to improve quality of the medicinal product in accordance with Part III of the Good Manufacturing Practice.

71. The manufacturing process should be monitored to ensure that it is operating as expected to produce the medicinal product quality attributes planned in the design space. Such monitoring may include an analysis of trends in the manufacturing process as additional experience is gained throughout routine

manufacturing. In case of particular design spaces involving mathematical models, their periodic maintenance may be useful to ensure model operation. Model maintenance is an example of an activity that a company may manage within its own internal quality system as long as the design space remains unchanged.

72. Once additional knowledge of the manufacturing process is gained, it may be necessary to expand, reduce, or reformulate the design space. Changes in the design space should be made in accordance with the Union authorities' acts on circulation of medicines.

VI. Providing the Pharmaceutical Development and Related Information in the Marketing Authorization Application in Common Technical Document (CTD) Format

73. Information on pharmaceutical development shall be included in Section 3.2.P.2 of the marketing authorization application. Other information obtained from pharmaceutical development studies may be allocated throughout the marketing authorization application in a number of ways. However, the applicant should make it clear in which part such different pieces of information are provided. In addition to what is included in the marketing authorization application, some particular aspects (e.g., medicinal product's life cycle management, continuous improvement) of these Guidelines are addressed within the applicant's pharmaceutical quality system in accordance with Part III of the Good Manufacturing Practice.

1. Quality Risk Management and Development of the Medicinal Product and its Manufacturing Process

74. Quality risk management should be applied at different stages of the medicinal product development and manufacturing process. Assessments used for guidance and providing rationale for development decisions may be included in the appropriate Sections 3.1.P.2 of the marketing authorization application. For example, risk analyses and functional dependencies, which link material and

manufacturing process parameters to critical quality attributes of the medicinal product, may be included in Sections 3.2.P.2.1, 3.2.P.2.2 and 3.2.P.2.3 of the marketing authorization application. Risk analyses, which link the manufacturing process design to the quality of the medicinal product, may be included in Section 3.2.P.2.3 of the marketing authorization application.

2. Design Space

75. As an element of the proposed manufacturing process, the design space(s) may be described in Section 3.2.P.3.3 of the marketing authorization application, which includes description of the manufacturing process and its control. If reasonable, additional information may be provided in Section 3.2.P.3.4 of the marketing authorization application which addresses control tools for critical stage and intermediates. Sections 3.2.P.2.1, 3.2.P.2.2 and 3.2.P.2.3 of the marketing authorization application are appropriate for summarizing and describing the medicinal product development studies and manufacturing process that serve as the basis for the design space(s). Dependence of the design space(s) on the general control strategy should be described in Section 3.2.P.5.6 of the marketing authorization application, which includes the rationale for the medicinal product specifications.

3. Control Strategy

76. It is appropriate to summarize the general medicinal product control strategy in Section 3.2.P.5.6 of the marketing authorization application, which includes the rationale for the medicinal product specifications. However, information on the starting material control and manufacturing process control tools should be provided in the relevant Sections of the marketing authorization application (e.g., active pharmaceutical ingredient (3.2.S), control of excipients (3.2.P.4), description of the manufacturing process and types of manufacturing process control (3.2.P.3.3), control of critical stages and intermediates (3.2.P.3.4)).

4 Information on the Active Pharmaceutical Ingredient

77. If critical quality attributes of the active pharmaceutical ingredient have any potential to affect the critical quality attributes or the manufacturing process of the medicinal product, it is appropriate to provide an analysis of quality attributes of the active pharmaceutical substance in the Pharmaceutical Development Section of the marketing authorization application (e.g., Section 3.2.P.2.1).

ANNEX No. 1

to the Guidelines on Pharmaceutical
Development of Medicines

CHARACTERISTICS
of Differences between Minimal and Profound Approaches to Pharmaceutical Development

The Table below illustrates some of the potential differences between a minimal approach and a profound quality-by-design approach with respect to different aspects of pharmaceutical development and medicinal product's life cycle management. The comparisons are provided solely to improve understanding of the range of potential approaches to pharmaceutical development, so they should not be considered exhaustive ones. The Table is not intended to purposely state the only possible approach a medicinal products manufacturer may choose. The profound approach does not necessarily establish a design space or use real-time release test. Current practices in the pharmaceutical industry vary and typically fall between the two approaches provided in the Table below.

Aspect	Minimal approaches	Profound quality-by-design approaches
Pharmaceutical development in general	mostly empirical one; design studies are often performed for one variable at a time	a systematic approach that relates mechanistic understanding of starting material attributes and manufacturing process parameters to critical quality attributes of the medicinal product; multifactorial experiments for understanding the intended use of the medicinal product and the manufacturing process; establishing a design space; use of process analytical technology tools
Manufacturing process	fixed; validation is predominantly based on initial full-scale batches;	adjustable within the design space; a life-cycle approach to validation and, at its best, continuous manufacturing process verification;

	focus on optimization and reproducibility	focus on control strategy and sustainability; use of statistical process control methods
Manufacturing process control	in-process tests mainly for "passed (failed)" decisions (accepted (rejected)); off-line analysis	use of process analytical technology tools with appropriate direct and reverse control; manufacturing process operations are tracked and trends are built to support continuous improvement efforts after registration
Specifications for the medicinal product	major control methods; based on batch data available as of the registration date	part of the general quality control strategy; are based on the desired functional characteristics of the medicinal product with relevant supporting data
Control strategy	quality of the medicinal product is controlled primarily by testing intermediates (in-process materials) and the final product	quality of the medicinal product is delivered by a risk-based control strategy for well-understood characteristics of the medicinal product and the manufacturing process. Quality control tools are being shifted to early stages with the possibility of real-time release tests or reduced final product tests
Life cycle management	reactive (i.e. problem solving and corrective actions)	preventive action; promoting continuous improvement

ANNEX No. 2

to the Guidelines on Pharmaceutical
Development of Medicines

E X A M P L E S
of Applying Pharmaceutical Development Tools

I. Risk Assessment Tool

An interdisciplinary team of experts may jointly develop an Ishikawa (fish skeleton) Diagram (Fig. 1) to identify potential variables that may affect the desired quality characteristic. The team may then rank the variables based on the probability, severity, and detectability by using the failure modes and effects analysis (FMEA) or similar tools based on previously acquired knowledge and initial experimental data. Experimental design or other experimental approaches may then be used to assess the effect of high ranking variables, achieve a better understanding of the process flow, and develop an appropriate control strategy.

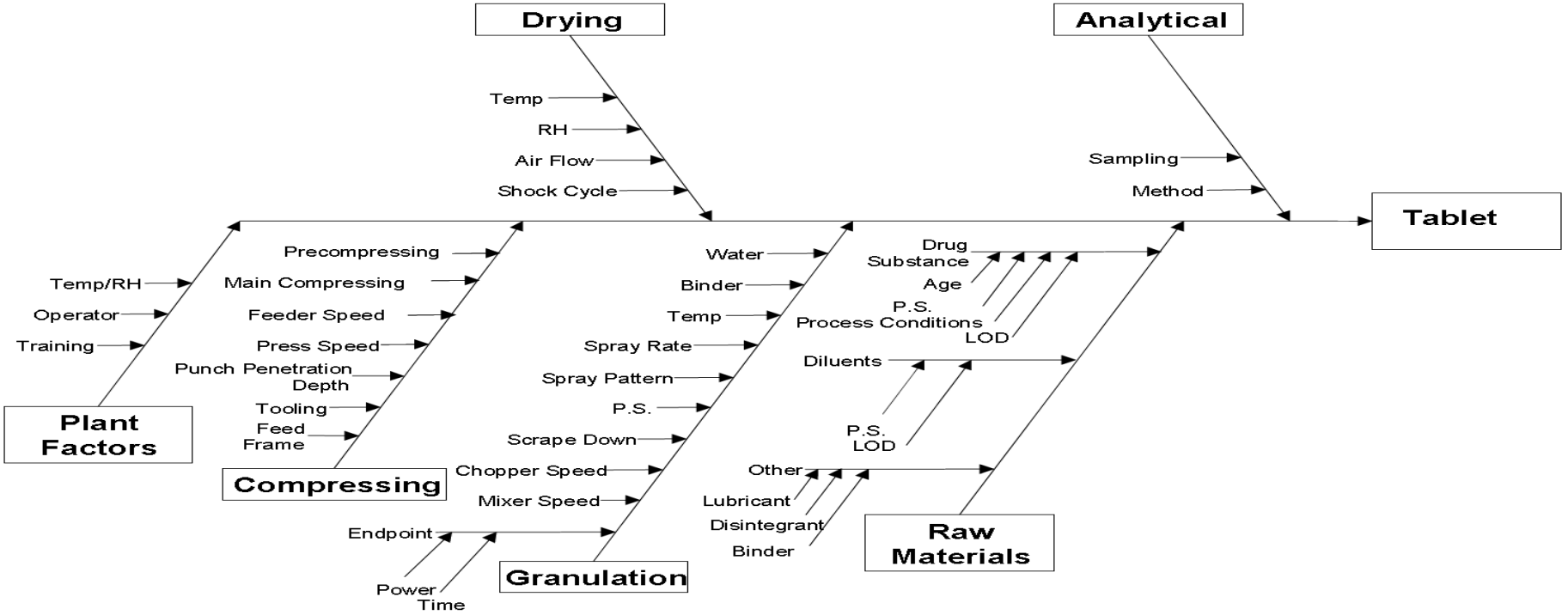

Fig. 1. Ishikawa Diagram

II. Reflection of Interactions

Figure 2 illustrates the availability or absence of effect of interactions between the three process parameters on the content of degradation product Y. The figure shows a series of two-dimensional charts illustrating the effect of interactions between three process parameters (initial moisture content, temperature, average particle size) of drying granulate (intermediates of the medicinal product) on degradation product Y. The relative slopes of the lines or curves on the chart indicate the availability of interaction. In this example, the initial moisture content and temperature interact, but the initial moisture content and average particle size do not, nor do the temperature and average particle size.

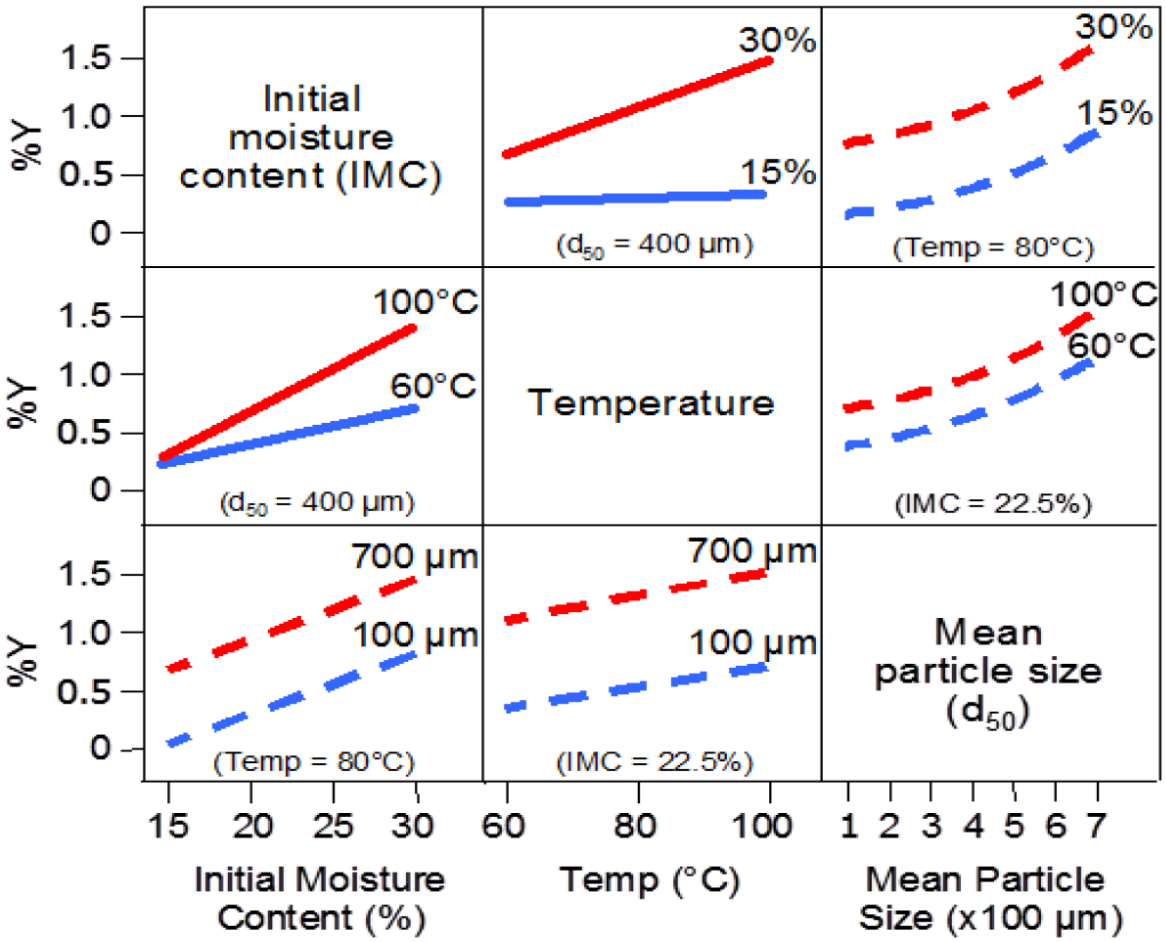

Fig. 2. Charts of effect change in technological parameters on the content of impurity in the formulation of the medicinal product

III. Representing the Design Space

Example 1. Graphs of degree of the active ingredient release are depicted as a surface chart (Fig. 3) and a contour chart (Fig. 4). Parameters 1 and 2 are factors of the granulation operation that affect the degree of the active ingredient release from the tablet (e.g., excipient characteristics, water content, granule size).

Two examples of potential design spaces are provided. The design space in Figure 5 is given by a nonlinear combination of parameter ranges that affect the degree of the active ingredient release. In this example, the design space is expressed by using a release rate surface equation solved within the parameters of an acceptable release rate (i.e. 80%). The acceptable range of one parameter depends on the value of the other, e.g.:

if the value of parameter 1 is 46, the range of parameter 2 is set between 0 and 1.5;

if the value of parameter 2 is 0.8, the range of parameter 1 is set between 43 and 54.

The approach described in Figure 5 maximizes the operating range to achieve the desired degree of release. In Figure 6, the design space is determined by a smaller range based on a linear combination of parameters:

the range of parameter 1 is set between 44 and 53;

the range of parameter 2 is set between 0 and 1.1.

Since the approach represented in Figure 6 is more restrictive, the applicant is free to choose it due to the simplicity of the operation.

In this example, only two parameters are considered, so they may be easily represented graphically. If there are several parameters, the design space may be represented for two parameters — in a manner similar to the examples presented above — at other values (e.g., high, medium, low) within the range of the third parameter, fourth parameter, etc. Alternatively, the design space may be expressed mathematically by using equations that describe the dependencies between parameters for a successful operation.

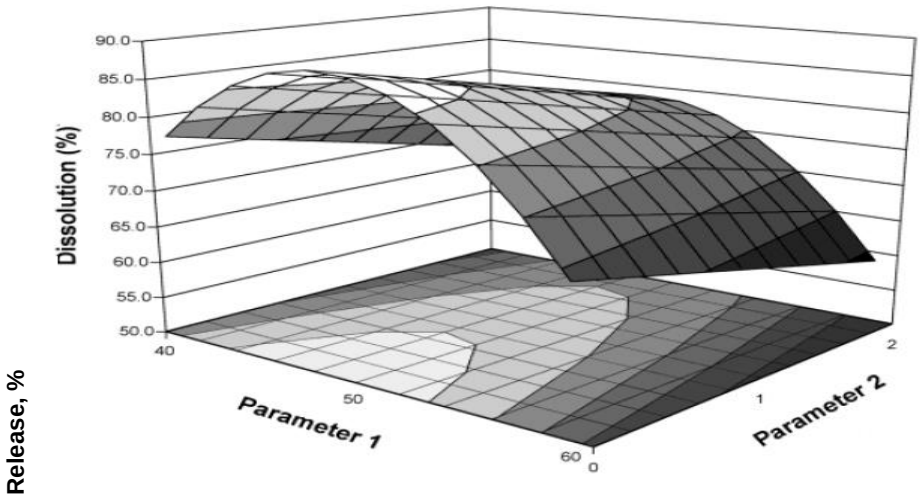

Fig. 3.
Response surface plot of dissolution as a function of two parameters of a granulation operation. Dissolution above 80% is desired.

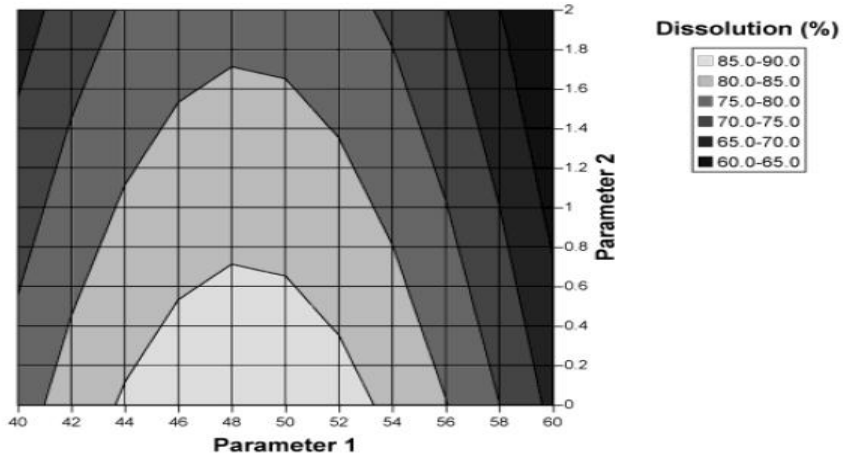

Fig. 4
Contour plot of dissolution from Example 1

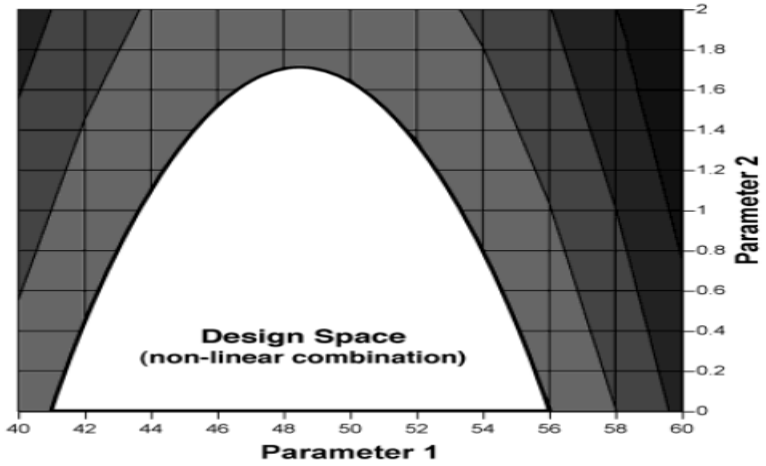

Fig. 5.
Design space for granulation parameters, defined by a non-linear combination of their ranges, that delivers satisfactory (i.e. >80%).

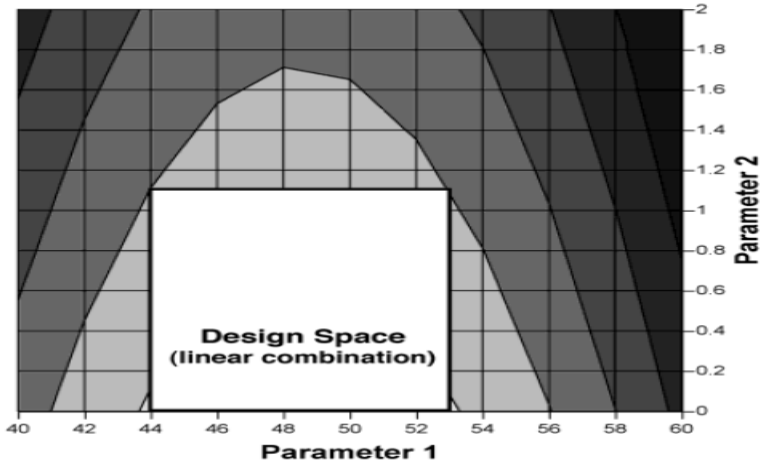

Fig. 6.
Design space for granulation parameters, defined by a linear combination of their ranges, that delivers satisfactory dissolution (i.e. >80%).

Example 2. The design space is determined on the general area of successful operational ranges for several critical quality attributes. The links of two critical quality attributes, namely tablet friability and active ingredient release rate, with two granulation process attributes are shown in Figures 7 and 8. Parameters 1 and 2 are factors of the granulation operation that affect the degree of the active ingredient release from the tablet (e.g., excipient characteristics, water content, granule size). Figure 9 shows the overlap between these areas and the maximum ranges of the proposed design space. The applicant may select the entire area or some part of it as the design space.

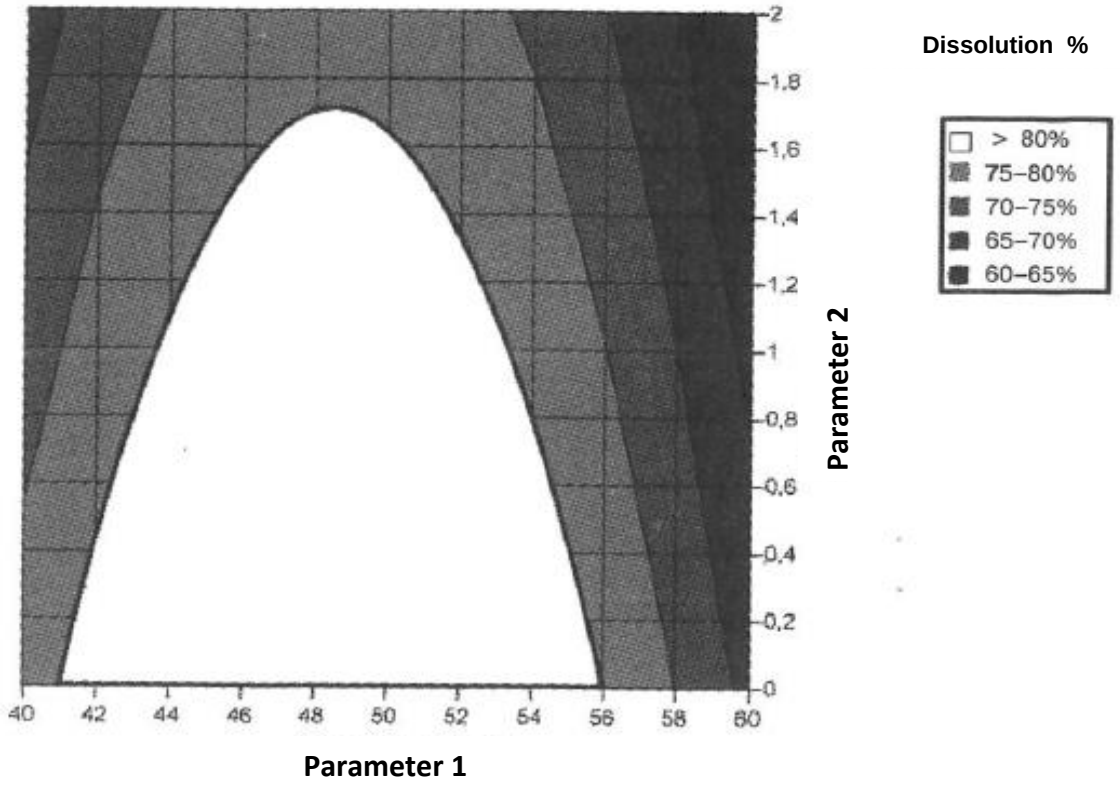

Fig. 7. Contour plot of dissolution as a function of parameters 1 and 2

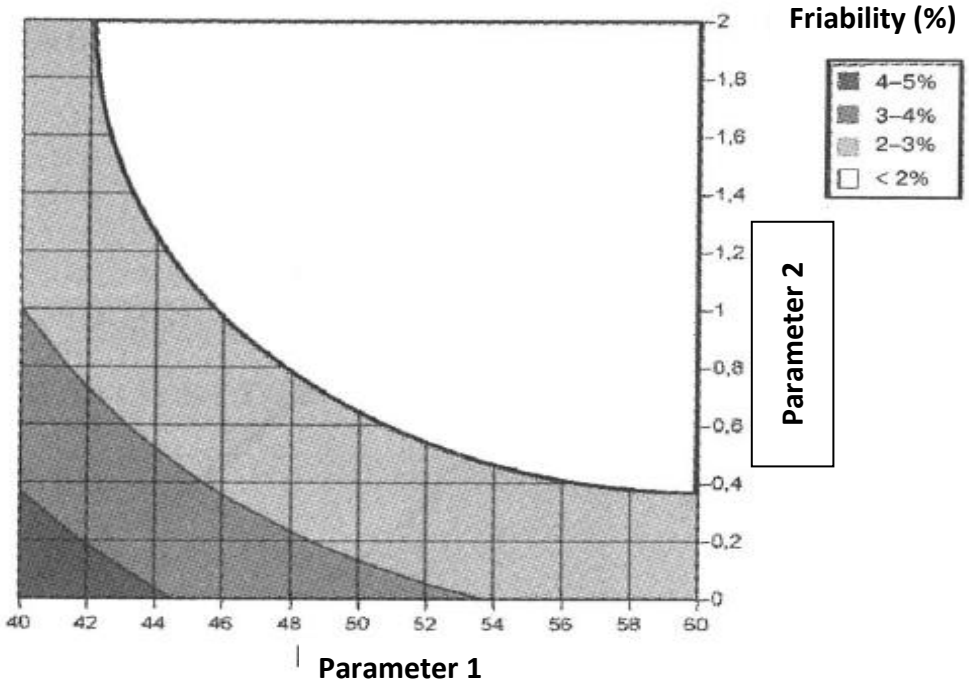

Fig. 8. Contour plot of friability as a function of parameters 1 and 2

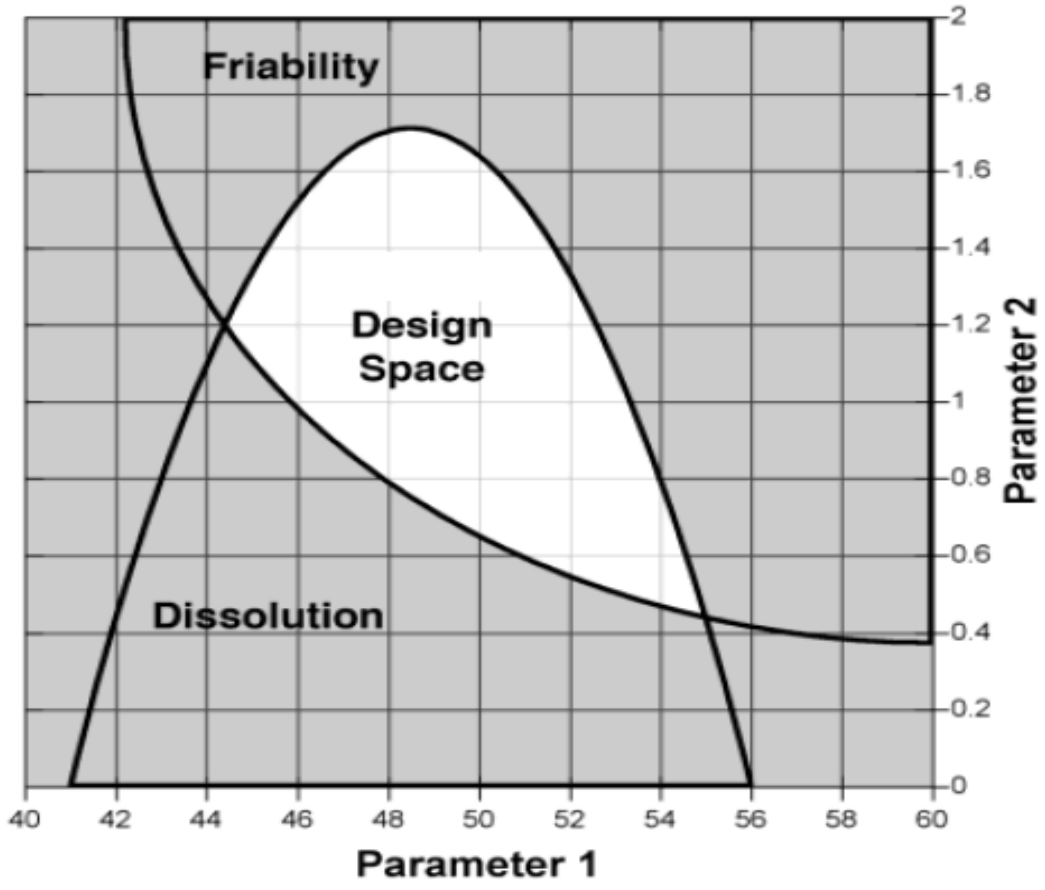

Fig. 9. Proposed design space, comprised of the overlap region of ranges for friability and or dissolution

Example 3. The design space for a drying operation that depends on temperature and/or pressure dynamics over time. The end point for moisture content is 1 – 2%. Operating above the upper limit of the design space may result in excessive impurity formation, and operating below the lower limit of the design space may result in excessive particle friability.

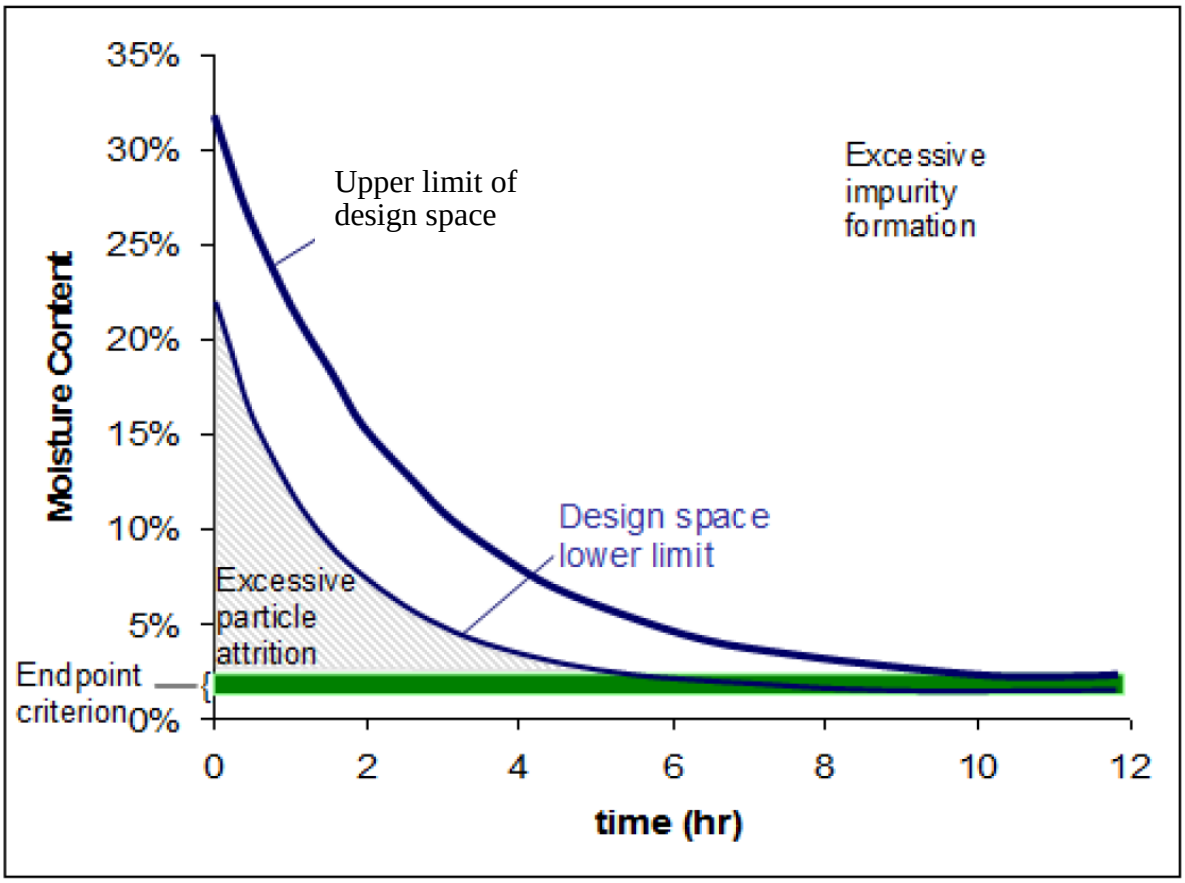

Fig. 10. Design space of effect of temperature and/or pressure changes over time on residual moisture content