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► To cite this version:

Saïna Hassanzadeh, Didier Gourc, François Marmier, Sophie Bougaret. Decision-making under uncertainty in drug development. PROJECT PERSPECTIVES, 2012, 34, p.40-45. hal-01847754

HAL Id: hal-01847754

<https://hal.science/hal-01847754>

Submitted on 7 Nov 2018

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Decision-making under uncertainty in drug development

In pharmaceutical industry, decision-makers have to decide whether to continue drug development projects, if the tests results on new compounds are good enough. Such decisions are made collectively, under a high degree of uncertainty and in non-emergency situations. These projects are very expensive, risky, and long. The major problem in this context is indecision. In order to improve the decision-making process in practice, we need to characterize and analyze situations of decision-making under uncertainty. In this paper, we propose a new definition of uncertainty that takes human factors in its characterization into account. Then, the factors that contribute to generate, characterize, perceive or process uncertainty are structured in a typology. That helps us recognize and explore causal and influential factors of uncertainty. Additionally, based on interview results, we present a description of the decision-making process in pharmaceutical R&D, illustrating the role of different actors, their interactions, and the flow of information. This should help decision-makers adopt proactive practices instead of reactive ones.

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Introduction

Decision-making in R&D faces much uncertainty in all industries. The development of new products implies dealing with uncertainty that comes from innovation in product development process, market dynamics, and changes in regulation. Many questions need to be answered in order to make decisions during the development project. In pharmaceutical industry, the degree of uncertainty is particularly high, since even if many tests are performed on animals, the behavior of the new compound in human body cannot be known.

A drug development project is defined as a process that allows a presumably active chemical or biological entity to become a pharmaceutical drug. After passing a series of tests, the drug is certified for commercialization, guaranteeing its safety, efficacy, and quality (Gourc & Bougaret 2000). Drug development projects are composed of different phases, separated by Go / No Go decision milestones, wherein a steering committee decides whether to continue or stop the project. These decisions are based on project status information and the results of the studies which are generally very poor compared to what is required to make an informed decision in optimal conditions.

Drug development projects last an average of 13.5 years and cost about \$ 873 million, with a success rate of only 4% (Paul et al. 2010). The cause of this high attrition rate is not related to the lack of management of time, costs, and resources. Planning is a crucial, difficult, and necessary task for project success but it is not sufficient. There are unclear zones that we are not able to recognize at an early phase of a project (Perminova et al. 2008). In drug development, the main reason of this high attrition rate is the lack of knowledge about the safety, efficacy, and quality of the molecule during the first phases of the project. In a full 50% of lately stopped projects, failure is due to lack of

efficacy, 30% to lack of safety and 20% are not safer nor more effective than the drugs already available on the market (Gordian et al. 2006).

In this context, decision-making process is characterized by: 1) a strong degree of uncertainty: when the profits and risks are unknown, as it is usually the case in drug development projects, the degree of uncertainty is high and the choice is difficult, 2) non-emergency situations: in R&D, decisions to be made do not seem urgent, comparing accident, crisis, and disaster contexts, but a potential danger could arise in the future. Previous research works concentrate on risk and uncertainty in emergency situations, but for the first time, to the best of our knowledge, ours considers non-emergency situations, wherein it is quite possible to postpone the decision, waiting for complete and accurate information. Situations in which decisions may appear without urgency include the choice of investments, renewal and modernization of equipment, and the introduction of new safety devices, 3) the collective aspect: individual differences within a group play a crucial role in interactions between experts and could complicate the decision or indecision processes and engender or increase uncertainty.

The structure of the paper is as follows. First, we review two major approaches to define and identify uncertainty: the objective approach and the subjective approach. We present our definition, which includes both subjective and objective aspects contributing to uncertainty identification. Next, we present a typology of uncertainty factors related to the subject, object and context. Then, we review how decision-making process is defined in the literature and present our description of decision-making process in drug development. Our description is illustrated by a case study based on a real application.

State of the Art

Defining and identifying uncertainty

The most fundamental capability of human beings is conscious decision-making. In order to better understand decision-making process, we need to understand the notion of uncertainty first (Kir 2005). Economists are interested in defining uncertainty in order to identify and control it. In economics, uncertainty is defined either based upon the impossibility of calculating probabilities as in the Knight's definition, wherein uncertainty is defined as a situation in which it is not possible to specify numerical probabilities (Knight 1921), or by emphasizing the lack of information in a more general sense (Galbraith 1973; Thiry 2002; Kir 2005).

Psychologists and sociologists define uncertainty either through a state of mind characterized by "doubt, or a conscious lack of knowledge about the outcome of an event" (Head 1967), or through its consequences: "uncertainty is the inability to act deterministically" (Thompson 1967), "uncertainty is a sense of doubt that blocks or delays action" (Lipshitz & Strauss 1997). In psychology, "in the contrast to the decision theory approach, psychological uncertainty is not a part of the external environment, such uncertainty may be a mental reaction to the external environment, but it is a psychological phenomenon existing only within the mind of the person who doubts" (Head 1967).

In economics, uncertainty is characterized by the lack of information about events and human factors are not taken into account. Thus, in this context, uncertainty is objective and exists independently of the existence of an uncertain subject. In contrast, in psychology, the emphasis is on human's mental state and uncertainty is relative to a subject.

Similar to scholarly definitions of uncertainty, dictionaries often define uncertainty either by emphasizing the object or the subject. For example, the Cambridge dictionary defines uncertainty by emphasizing the object: "when something is not known", whereas Webster focuses on the subject: "the state of being unsure of something". Objective and subjective approaches are also identifiable in philosophers' literature. Aristotle, Descartes and Laplace only admit logic and mathematical rules to construct certainty. Socrates, Plato, Carneades, Pascal and Kant accept other ways of certainty construction such as faith and emotion.

When a subject is uncertain about an object, where does the uncertainty come from? Is it in the subject's mind or does it come from the unpredictability of the object's comportment? We think it is important to take human factors into account

in the characterization of uncertainty. In our definition, **uncertainty is a subject's conscious lack of knowledge about an object which is not yet clearly defined, in a context requiring a decision.** Uncertainty cannot be defined neither as only pertaining to the subject nor to the object, because a subject could be uncertain about an object, while another subject is certain about it. Hence, uncertainty is a relationship between subject and object.

Furthermore, context is an important factor in defining uncertainty. A subject could be uncertain about an object but if he does not need to make a decision nor perform an action, this situation is not considered to be an uncertain situation. For example, I am not sure whether the laboratory building is accessible during the weekend or is closed due to construction, but since I do not plan to go there this weekend, this situation does not concern me. This definition of uncertainty includes the three elements that contribute to the identification of uncertainty: subject, object, and context.

Typology of uncertainty factors

Figure 1 outlines the main categories of the factors that contribute to generate, characterize, perceive or process uncertainty. This typology is based on three axes of the uncertainty definition: subject, object, and context: 1) factors of uncertainty related to the subject are divided into two sub groups: the subject's psychological traits and his professional experiences as individual factors and contradictory opinions and debates as collective factors, 2) factors of uncertainty related to the object refer to two sub groups: the states of the object that are dynamic and the goals of the subject that depend on the object's states, 3) factors of uncertainty related to the context also refer to two sub groups: internal factors such as the organizational and hierarchical factors which do not favor the circulation of information inside a company and could increase the level of uncertainty. Likewise, external factors exist such as market dynamics, competitors' activities, stakeholders' expectations, regulatory changes, and doctors' conviction in a new drug, which make the environment of decision uncertain.

The comprehensive vision of this typology helps us understand the sources and the influential factors of uncertainty associated with the manager and the project team (subject), with the project (object), and the environment (context) of the decision. This allows us to control some of the uncertainty sources in order to reduce it as much as possible and deal with what remains according to the type of the source.

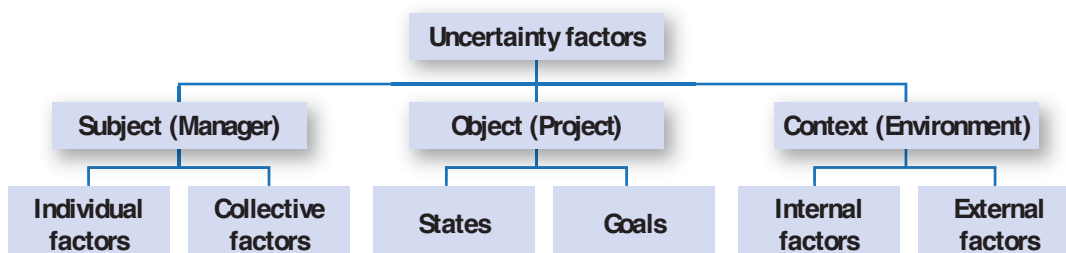


Figure 1. Our typology of uncertainty factors

Decision-making process under uncertainty

Decision-making is an important part of any organization (Panneerselvam 2006). Simon has suggested that "a decision is not an *act*, but a *process*" (Tsoukiàs 2008). The process involves selecting the best among several options through a proper evaluation of the parameters of each option and its consequences (Panneerselvam 2006). However, "all decision is a matter of compromise. The alternative that is finally selected never permits a complete or perfect achievement of objectives, but is merely the best solution that is available under the circumstances" (Simon 1947). Generally, decision is the result of interactions between preferences of individuals. The decision process mainly consists in these interactions, under the various compensating and amplifying effects of the system that make up what we shall call the decision process (Roy 1996).

The decision-maker usually chooses an option based on the balance of benefit / risk of available options. If he knows all the possible options and their consequences, he is in the case of a deterministic decision. For example, in maintenance management, if the annual maintenance cost and the annual operating cost of equipment are known in advance and are not subject to any change in the future, then the decision about the economic life of the equipment is a deterministic decision (Panneerselvam 2006). In the case of non-deterministic or decision under uncertainty, information about different choices and their consequences is partial for the decision-maker. The degree of uncertainty could be different. This difference corresponds to the difference between required information and available information.

A decision-making iterative process in four stages has been proposed by Simon: *Intelligence stage* as the first stage comprises information collecting and problem identifying, *Design stage* centers on an alternative analysis and construction (invent, develop, and analyze), *Choice stage* focuses on alternatives evaluation, and *Review stage* consists of evaluating earlier decisions and satisfaction level (Simon 1977). Janis and Mann propose a vigilant decision-making process which takes into account any new information or expert judgment to support the choice process (Janis & Mann 1977). Based on these two processes, in the next section, we propose a global vision of decision-making under uncertainty in drug development projects. The objective is highlighting the role of different actors and the flow of information.

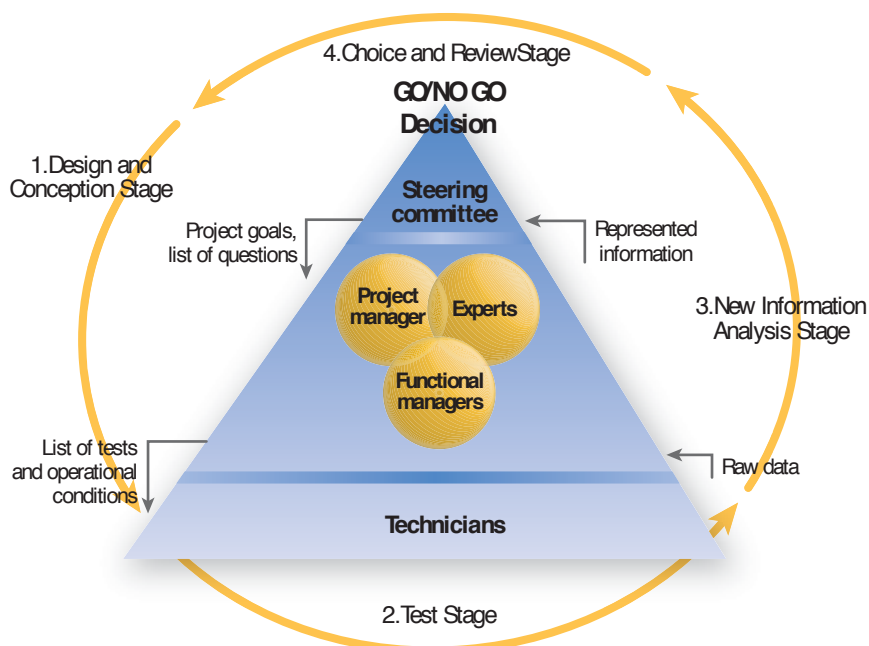


Figure 2. Global vision of decision-making process in drug development projects.

Decision-making process in pharmaceutical R&D

Global vision

Figure 2 represents two dimensions in decision-making process: the actors with their positions in a pyramid form and the flow of information in italic font. We distinguish four macro-stages in the decision-making process: 1) Intelligence and Design stage, 2) Test stage, 3) New Information Analysis stage, and 4) Choice and Review stage. The first stage, which corresponds to Simon's model (Simon 1977), includes problem identification, information collection, and solutions development. The steering committee needs information about molecule activity and behavior in human body, in order to decide whether or not to continue the project. Project goals and a list of questions about the characteristics of the molecule are transmitted to the project team in charge of defining the Target Product Profile (TPP) as a key strategic tool, which guides drug development. TPP is the key design template for creating the development plan and should be defined by the project team as it is a multidisciplinary task (Kennedy 1998). Focusing on the TPP, the project team determines a list of tests and operational conditions for technicians.

The second stage corresponds to the fourth stage of Janis and Mann's model: searching new information relevant to the choice. In this stage, the technicians carry out the tests and provide the raw data (Janis & Mann 1977). The third stage corresponds to the fifth and

sixth stages of Janis and Mann's model: "taking account of any new information or expert judgment, even when the information does not support the initial choice of course of action and re-examining the positive and negative consequences of all known alternatives, including those originally regarded as unacceptable, prior to making a choice" (Janis & Mann 1977). In this perspective, the raw data will be interpreted by functional managers. Project managers and experts contextualize the information depending on the project goals and consult functional managers to carry out the new tests, if necessary. Finally, the contextualized result of the tests will be presented to the steering committee. The last stage corresponds to Simon's model during which the steering committee, using a benefit / risk analysis, will decide whether to continue or not.

In the first two stages, the project managers more or less know which questions must be answered in order to obtain the authorization of commercialization (European Commission 2008). However, the hypotheses about the molecule are not yet verified by the tests. Thus the factors related to the object (project, new molecule) play an important role in creating and processing uncertainty. But in the last two stages, we have to interpret, analyze, contextualize, and represent the acquired information and the role of the subjects (project manager and the experts) becomes crucial. A more detailed version is presented in the next section, emphasizing the last two stages.

Detailed vision

Figure 3 illustrates a detailed vision of decision-making in drug development projects. We use the Business Process Modeling Notation (BPMN), which is a standard graphical notation. This diagram illustrates the interactions between the different actors and shows the flow of information from the top to the bottom of the pyramid and vice versa. We focus on the new information analysis stage of the decision-making process.

At the end of each phase, several options exist. If the results of studies are sufficiently good and demonstrate the objectives of the phase such as efficacy for animals in preclinical phase, the decision will be to continue or accelerate the transition to the next phase (tests on humans). If the results are not adequately satisfying, the steering committee, consulting the project team, requests to perform the new tests which clarify and complete the previous results. Depending on the situation, it is possible to postpone the Go / No Go decision waiting for the new results or to start the next phase and review the decision when the new results arrive. If the results are bad and prove the inefficacy or the toxicity of the molecule, the project will be stopped.

During the whole process, we find examples of the three types of uncertainty factors. During the interpretation of data, the factors related to the object (molecule) play an important role in creating uncertainty, especially

by incompleteness or contradiction of information. Factors related to subjects, especially individual factors, such as perception and reasoning are also important. During the contextualization of information, factors related to the context appear: internal factors, such as the condition of other projects in the pipeline and external factors such as market dynamics.

During the representation of information, the role of subjects in the communication of results is crucial. At the end, during the Go / No Go decision, factors related to subjects, especially collective factors, such as debates and different ideas about the doubtful results contribute to creating uncertainty. There are two major problems in such a human-in-the-loop system: the loss of information and the subjectivity of interpretation and representation, on the right-hand side of the pyramid. This description helps us obtain an understanding of the decision-making process, which is essential to improve these practices.

Application case

Many questions need to be answered to prove the safety, efficacy, and quality of a molecule in order to obtain the authorization of commercialization. The toxicity of the molecule, its stability, clinical and side effects, mechanism of absorption and distribution in human body, and elimination from it are a few examples of these questions. In the decision pyramid, we consider

the stability question as a part of the quality question: is the product stable under conditions of usage? Many environmental factors affect the stability of the product.

Depending on the project goals and also the available quantity of the product, the project team establishes a list of tests to be conducted in order to obtain data on product degradation in different climatic zones. Operational conditions such as temperature, humidity, and light are also determined, so that the real packaging and storage conditions are simulated. A protocol that includes this information and also the study number, quantity of the product, time intervals, measurement, and analysis methods have to be followed by technicians. Table 1 presents a simplified part of the results. At time $t_0 + 12$ months, technicians register -0.05% of degradation in ambient temperature.

The functional manager's interpretation is that our molecule is approximately stable. The project team contextualizes this interpretation in terms of project goals and tries to answer the following questions: does this degradation rate impact the efficacy of the molecule in usage conditions? Could the degradation rate be reduced in another container such as a blister? In relation to the results of other studies, such as toxicity, is this degradation rate acceptable? Thus, after all these tests and studies, many questions remain without certain answers.

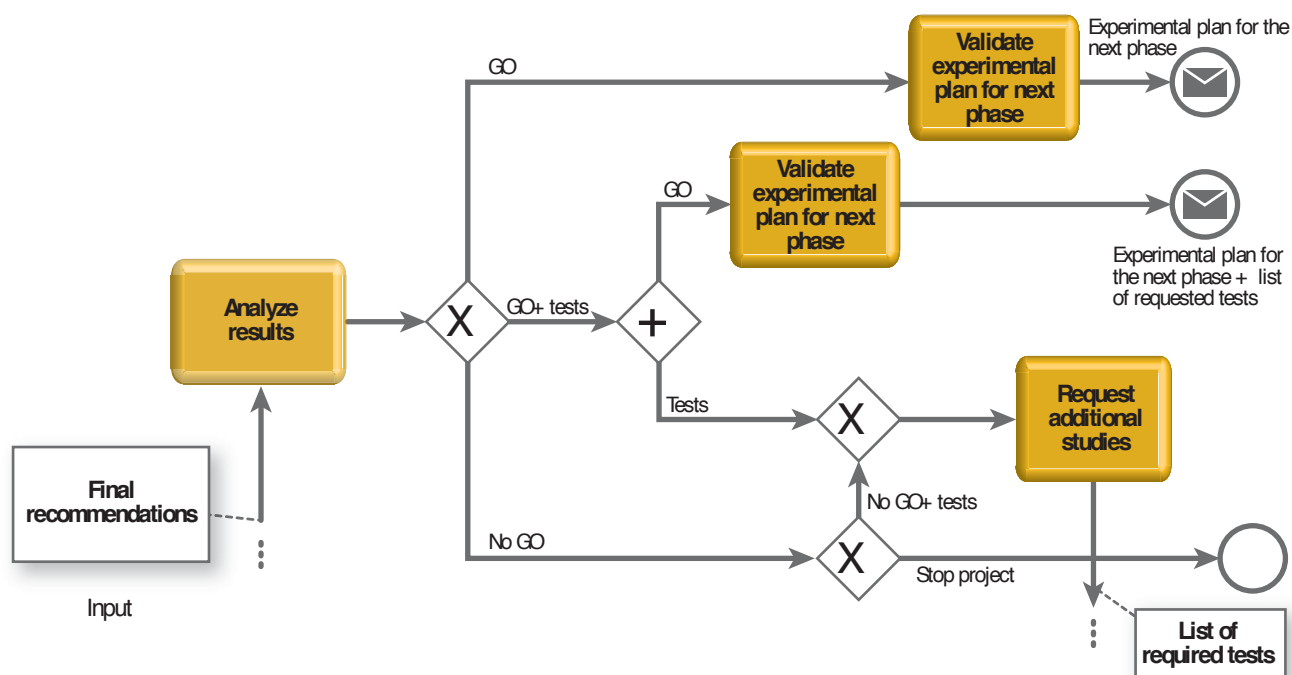


Figure 3. Detailed vision of decision-making in drug development projects.

Time/ Temperature	0°	5°	25°
t ₀	13 µg/l	13 µg/l	13 µg/l
t ₁ month	12,9999 µg/l	12,9999 µg/l	12,9995 µg/l
t ₆ months	12,9998 µg/l	12,9997 µg/l	12,9980 µg/l
t ₁₂ months	12,9997 µg/l	12,9995 µg/l	12,9935 µg/l
t ₁ month + H ₂ O		12,9994 µg/l	12,9945 µg/l
t ₆ months + H ₂ O		12,9993 µg/l	12,9942 µg/l
t ₁₂ months + H ₂ O		12,9991 µg/l	12,9934 µg/l

Table 1. Stability measurement tests

Conclusion

The comprehension of the notion of uncertainty is indispensable for understanding the decision-making process in situations where we do not have enough knowledge to decide. We distinguish two main approaches in defining uncertainty: the objective and the subjective approaches. We propose a new definition of uncertainty that allows these approaches to converge, including three key elements: subject, object, and context. From this point of view, we present a typology of uncertainty factors related to each element. This typology enables us to recognize and control some sources of uncertainty and offers a perspective to deal with causal and influential factors of uncertainty related to subject and context, which are less studied compared to uncertainty caused by object.

Decision-making systems in companies are the human-in-the-loop type systems. Thus, we cannot ignore the role of human factors in generating uncertainty and dealing with / handling it. In the description of the decision-making process in pharmaceutical industry we propose, the human aspect is in the center. We identify different levels of hierarchy in the decision-making system in a pyramid, highlighting the role of the subject and context in producing and dealing with uncertainty. In this pyramid, we illustrate the information flow in two directions: from the steering committee to the technicians and vice versa.

A practical example regarding the question of stability, as a small part of a larger question, the quality of the molecule, is presented. Many other questions have to be answered during the development project. Go / No Go decisions are based on these answers which are inexact and incomplete. This description is a first step to understand why decision-makers postpone decisions in such situations. A more complete model that offers a global vision of the project will be the next step of this research work.

Acknowledgements

This work was supported by the Foundation for an Industrial Safety Culture (Fondation pour une Culture de Sécurité Industrielle).

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