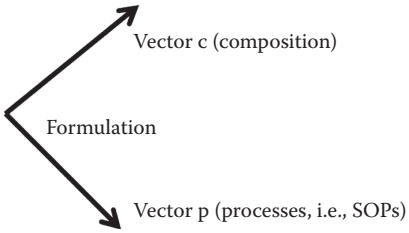

FIGURE 20.2 Simplified illustration (projected on two dimensions) of the formulation design space consisting of the vector composition ***c*** and of the vector pharmaceutical processes **p**.

It is an absolute necessity to harmonize the pharmaceutical technical equipment to minimize scale-up problems and, last but not least, to interpret rigorously the formulation design space. In accordance with ICH Q8 (ICH harmonized tripartite guidelines, http://www.ich.org) the formulation design space can be defined by two vectors: **c** = composition and **p** = pharmaceutical process (Figure 20.2).

The formulation design space facilitates the application of the *Right, First Time* concept by defining reasonable limits for the product specifications, that is, intermediate products such as granules, and final products such as capsules or tablets. In this context it is important to use the identical formulation design space from the very beginning of any development work up to registration of the medicinal product to be able to use all data. Thus, the classical workflow—starting with a simple capsule formulation as service dosage form for clinical phases I and II and development of the final marketed tablet formulation in clinical phase IIc for clinical phase III, registration and clinical Phase IV—should be replaced by *Right, First Time* workflow starting with the market-ready tablet formulation already at clinical phase I (Table 20.1) (Leuenberger et al., 2013).

Formulation Design Space

The formulation design space can be efficiently described by an experimental design. The number of factors to be evaluated depends on the knowledge and experience of the formulator with the API. It is evident that the formulator needs to know which excipients are chemically compatible with the API. In this context, a suitable factorial design should be used, that will enable the formulator to choose the right excipients showing—in addition—interactions, which may stabilize the API (API–excipient test program, Leuenberger and Becher, 1975). The API should be considered as the primary innovation, that is, as a jewel which needs to be cut and polished by choosing the right excipients to show its brilliance by an excellent bioavailability of the API and by a robust formulation. Thus, during the preformulation work, it may be necessary to perform not only a chemical but also a pharmaceutical-technological API–excipient compatibility program in order to select the optimal excipients for a chemical and technological robust formulation. For this purpose it makes

TABLE 20.1
Conventional Workflow versus *Right, First Time* Workflow

Conventional Workflow	*Right, First Time* Workflow
Clinical Phase I: development of a service dosage form, that is, a *simple* capsule	Clinical Phase I: development of market ready tablet dosage form instead of service form
Capsule redeveloped into a tablet for bioequivalence testing	Small-scale production
Scale-up exercise	Scale-up exercise (computer assisted)
Mass production of final marketed form	Mass production of final marketed form
Two-sigma quality	*Six-sigma* quality

Source: Leuenberger, H. et al., *Swiss Pharma*, 35, 4–16, 2013.