Use of DOE for Bioassay Development:

Results of surveys held in 2016 and 2017 by BEBPA

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Abstract

Results are presented from two surveys on current practices in the use of Design of Experiments (DOE) in bioassay development, one survey held at the 9th Annual BEBPA European Bioassay Conference, September 2016 and one held at the 1st Annual BEBPA USA Bioassay Conference, March 2017.

Introduction

Design of Experiments (DOE) permits a systematic assessment of the effect that various factors might have on the results of an assay. Over the last few years, it is being used increasingly in the field of biopharmaceuticals for the development of bioassays for potency testing. Study of multiple factors at various levels, such as component concentrations, temperature or timing, and interactions between these factors, represents an enormous investment of resources. Various designs have been developed to maximize the information obtained from a reduced number of experiments. For bioassays, DOE has been used mainly for robustness studies but it is a tool that can be used, offering significant potential benefits, throughout the entire bioassay development process.

To see to what extent and how DOE is currently being used in bioassay development, a survey was held at the 9th Annual BEBPA European Bioassay Conference, September 2016 (1) and at the 1st Annual BEBPA USA Bioassay Conference, March 2017 (2).

Survey Method

During the course of a conference session entitled "The Use of Quality-by-Design and DOE Tools for BioAssay Development" by Dr Laureen Little, questions on various aspects of the use of DOE in bioassay development were posed to the audience. The answers were collected using the Keypoint system (3). Each audience member received a transceiver. The data collected are linked to the transceiver number, but the transceivers were allocated randomly, so the responses were collected anonymously. Using the transceiver, each audience member could select the appropriate response from the set of options presented, and had the option of correcting a wrong response. Seconds later, the collated responses were displayed graphically to the audience.

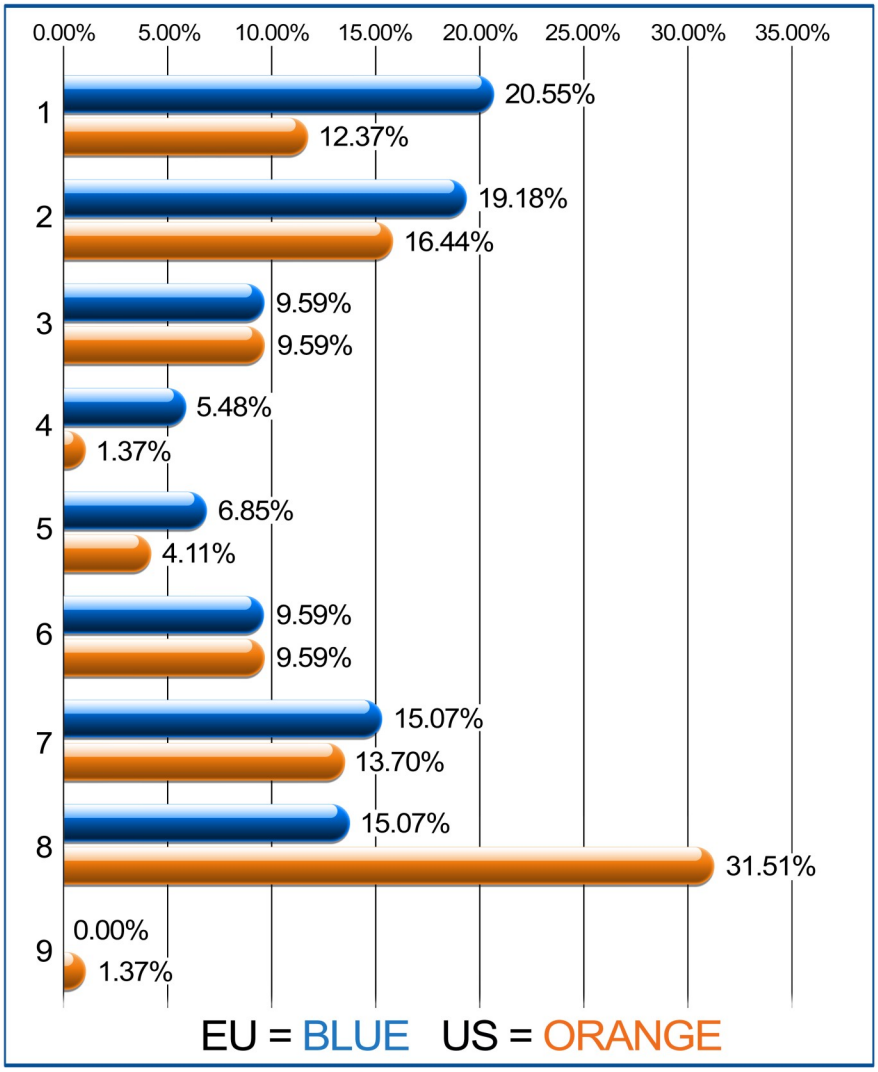
Survey Results

The survey in the USA was conducted a little over five months later than that in Europe, so some organizations may have changed their practice between the two surveys. For the 2016 European conference, there were 148 delegates potentially participating in the survey, representing 82 organizations; for the 2017 USA conference, there were 124 delegates representing 66 organizations. In the European conference 95 delegates participated in the survey, and in the US, 98 delegates participated. 22 individuals and 20 organizations were present at both conferences and may have caused some duplication in the responses. With large organizations, it is possible that the responses reflect the practice of only some parts of the organization.

The first questions established the types of organizations involved, the types of bioassay, and how the assays are developed and used. The complete set of questions and responses from the two conferences is shown in Appendix 1, while the questions concerning specifically use of DOE are shown, in addition, immediately below.

#8

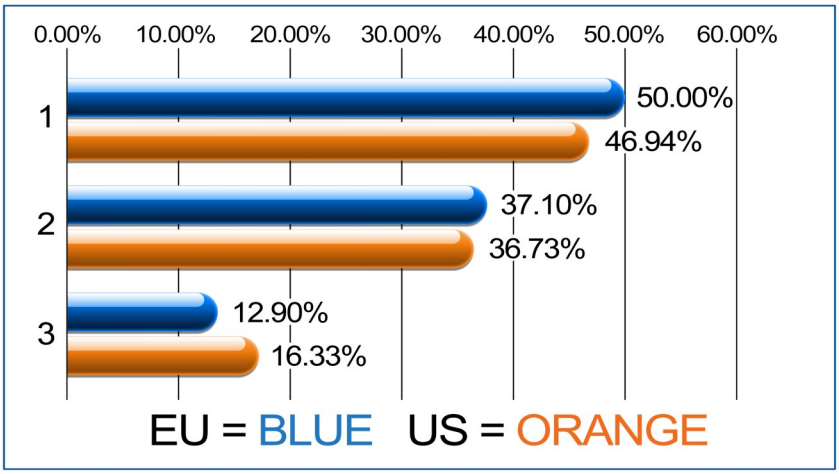
What is your current use of DOE?



European responses = 73
United States responses = 73

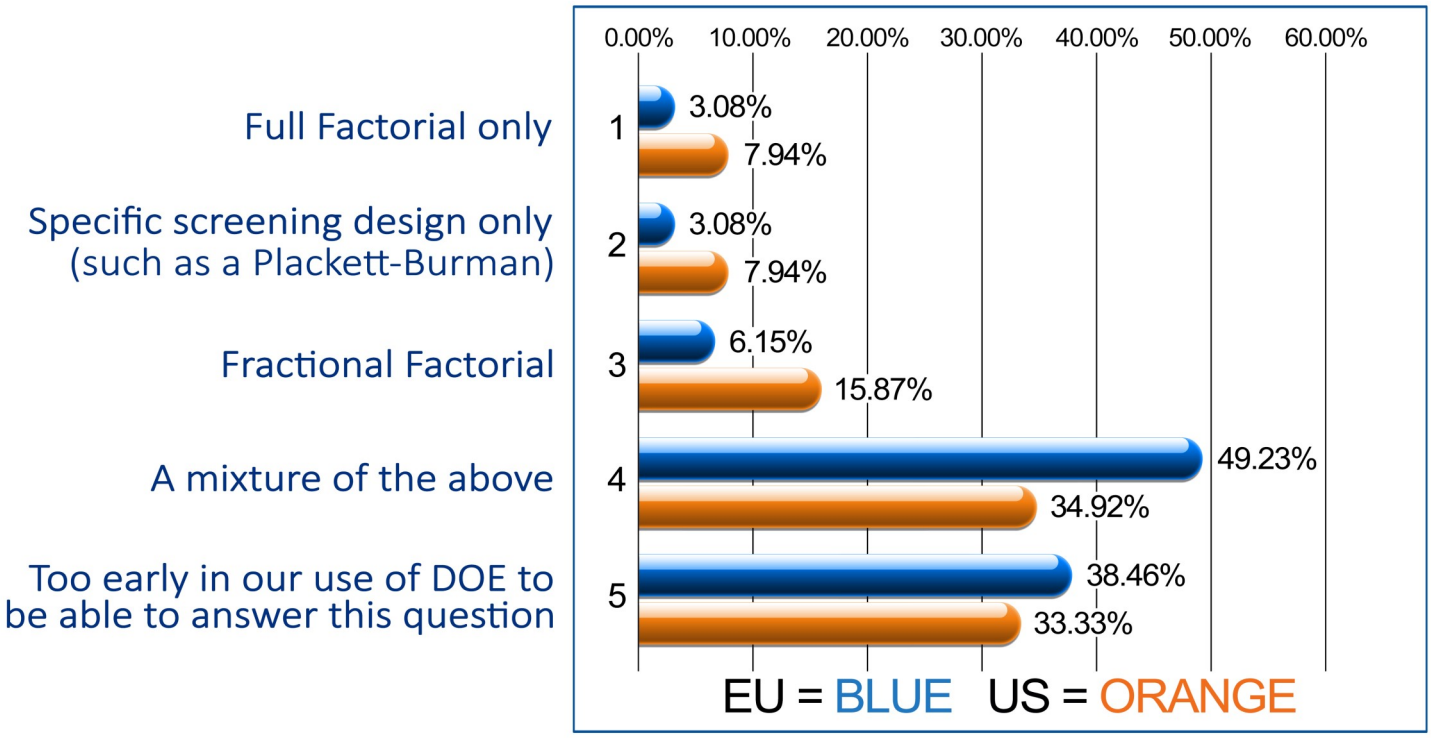
#9

How do you design your DOEs?



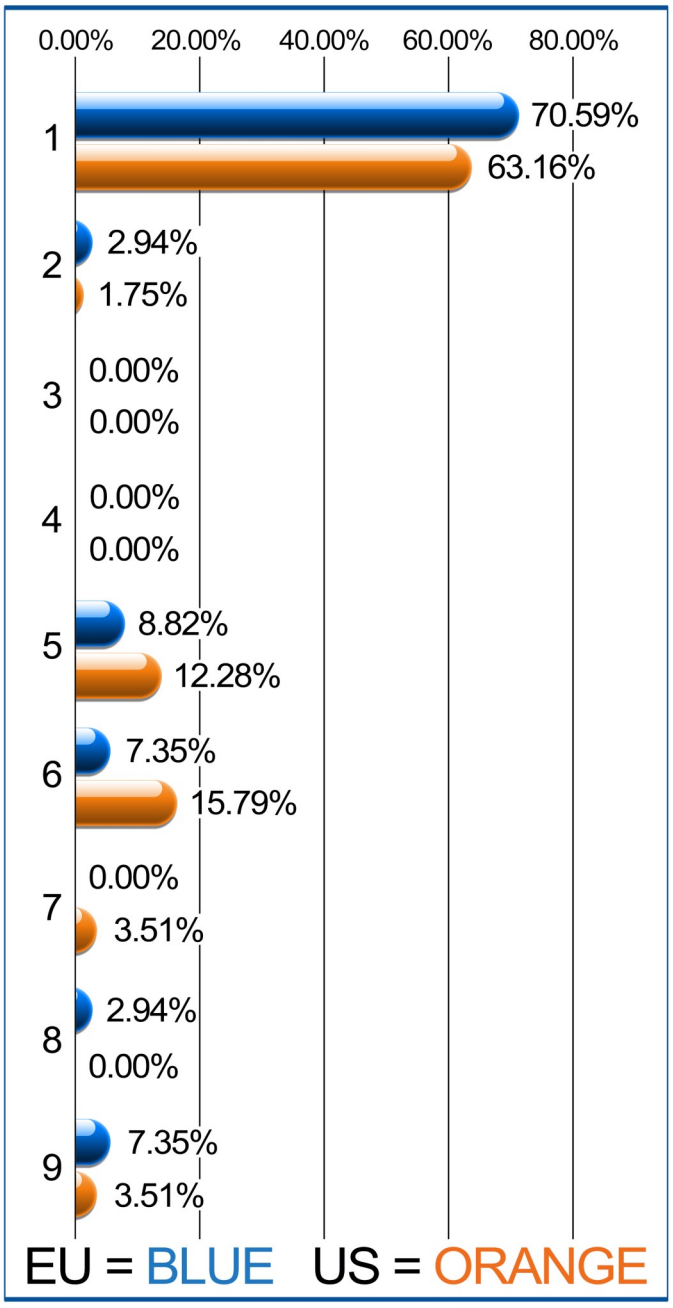
European responses = 62
United States responses = 49

What type of DOE designs do you use?



European responses = 62
United States responses = 49

Have you had any discussion on DOE with regulators?



European responses = 68
United States responses = 57

Use of DoE by different types of organization

	Contract		Small Biopharm < 50 employees		Mid Biopharm 50 – 300 employees		Global Biopharm		Consultant		Research Institute		Other	
	EUR	US	EUR	US	EUR	US	EUR	US	EUR	US	EUR	US	EUR	US
Total responses	**12**	**10**	**3**	**1**	**21**	**9**	**28**	**36**	**0**	**2**	**4**	**2**	**0**	**3**
Never use	3	1			9		2	3			1			2
Starting	4	3	1	1	4	1	4	7						
Robustness	1				1	3	2	3			1			
Trouble shooting					2		2							
Component optimization	1				2	1	2			1				1
Robustness + trouble shooting		1			1		6	5		1				
Robustness + component optimization			1		2	1	6	6			1	1		
Robustness + trouble shooting + component optimization	3	5	1			3	4	11			1	1		
Other								1						

Note: the total responses shown in this table (68 for the EUR survey, 63 for the US) are fewer than the total responses given to the question 8 on use of DOE (73 for EUR, 73 for US) because some respondents to the question did not state what type of organization they were

Observations

The responses obtained in the European survey (September 2016) and US survey (March 2017) are largely similar. Global pharmaceutical companies are the largest individual class of organization represented, followed by contract organizations and mid-size biopharmaceutical companies (50-300 employees). The mid-size companies accounted for a greater proportion of the responses in the European survey than in the US survey. Concerning where the bioassays are developed, over 40% of responses came from manufacturers reporting that the bioassay development is done entirely in-house, while about 30% reported it is done both in-house and in collaboration with a contract organization. About 40% of responses reported that the bioassays are used right through from preclinical development, through Phase 1, Phase 2, and Phase 3 into post-marketing. About 65% of responses were from organizations using a combination of cell-based functional and binding assays, with immunoassays forming the largest single class of binding assay.

There was some difference in the degree of use of DOE reported in the March 2017 US survey compared with the September 2016 European survey. In the European survey, about 21% of responses indicated that DOE was never used and about 14% indicated that DOE was used for all three of robustness, trouble shooting and component optimization. In comparison, the US survey showed 12% as never using DOE and 32% as using DOE for all three purposes. This may indicate a possible geographical difference in practice or a possible increasing adoption of DOE.

Whereas previously, for bioassays, DOE has been used mainly for robustness studies, in the European survey, of the responses reporting use of DOE, only 12% were for robustness testing only. A similar result of 11% was obtained in the US survey.

Table 1 shows a breakdown of the use of DOE by the different types of organization. It is noticeable that in the European survey, 43% of responses from mid-size biopharm companies (more highly represented in the European survey) report never using DOE, against none from the mid-size companies in the US survey. For the global biopharm companies, only 7% (European survey) and 8% (US survey) of the responses report never using DOE, but the US survey showed 31% positive responses for the use of DOE for all three of robustness, trouble shooting and component optimization, against only 14% in the European survey.

The answers to how DOE designs were developed (question 9) were similar in both surveys, with about half indicating that the organization had access to a statistician, either an employee or a consultant. Just under 40% used software and designed their own and the rest designed their own without using software. The majority reported either using a mixture of designs or that it was too early in their use of DOE to be able to say what designs they were using (question 10).

It appears that there had been little relevant discussion with regulators on the use of DOE during development of bioassays, and hence, little feedback (question 13).

One factor currently under investigation in the development of cell-based assays is the use of ready-to-use cells as these may offer improved assay performance (as well as logistical and economic advantages) compared with cells harvested from continuous cultures (4). Question 12 asked about current use of ready-to-use cells. The results are shown in Appendix 2.

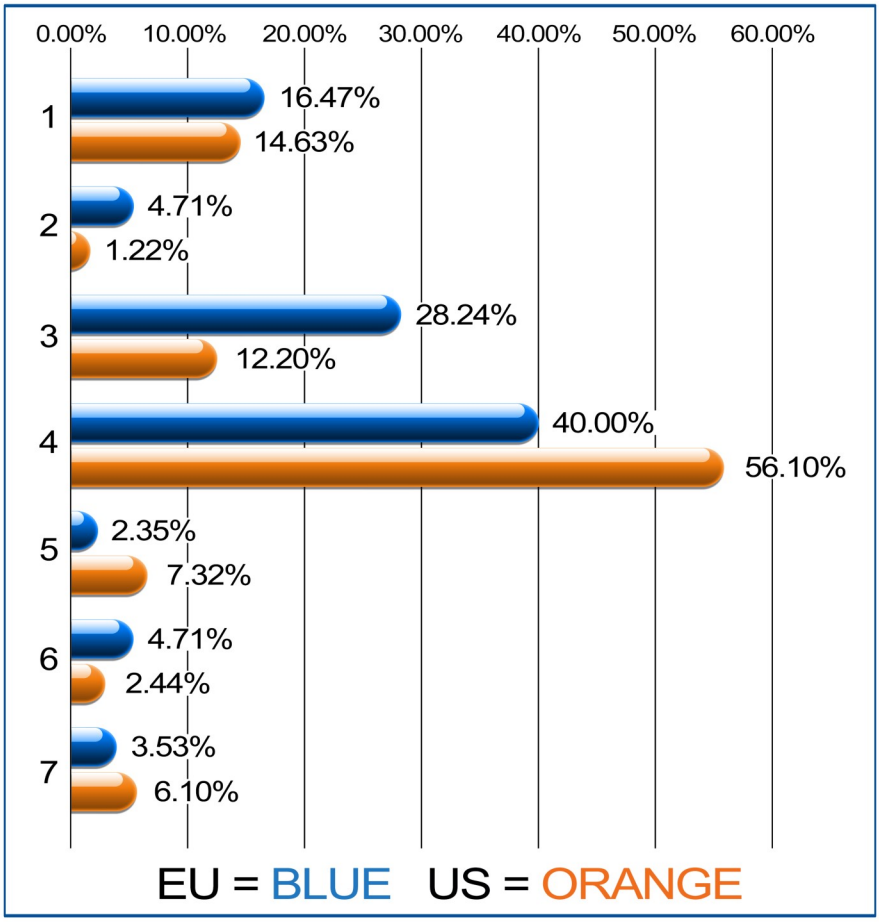
In summary

In the survey at the European meeting in September 2016, 79% of responses showed some use of DOE in bioassay development, with 19% of these just starting. In the survey at the US meeting in March 2017, 88% of responses showed some use of DOE in bioassay development, with 16% of these just starting.

References

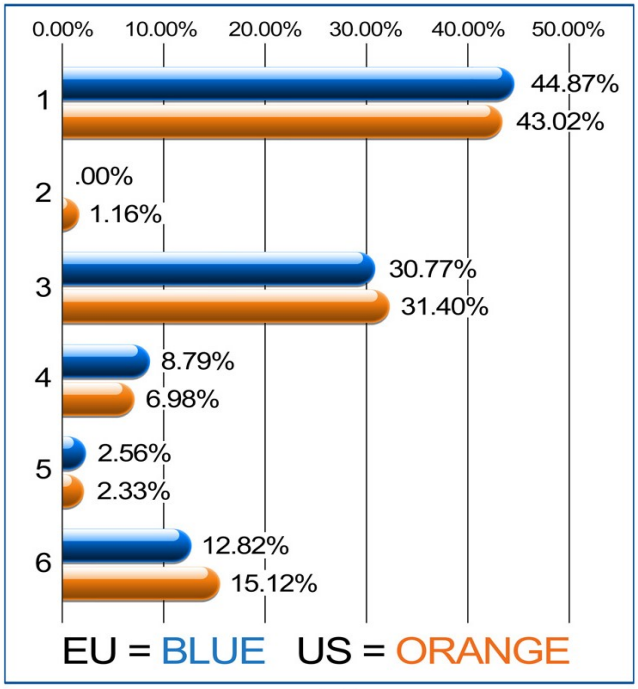
1) 9th Annual BEBPA European Bioassay Conference, 28-30 September 2016, Dubrovnik, Croatia
2) 1st Annual BEBPA USA Bioassay Conference, 8-10 March 2017, San Francisco, CA
3) Keypoint Interactive 2.3.31 Standard Edition, Innovision Incorporated, http://www.keypointinteractive.com
4) Ready-to-Use Cells in Bioassays for Quality Control of Biopharmaceuticals (2017) Robinson CJ & Lamerdin J; Bioanalysis Zone, *https://www.bioanalysis-zone.com/2017/05/19/ready-use-cells_spotlbioanalysis_of_biopharma/*

What type of company?



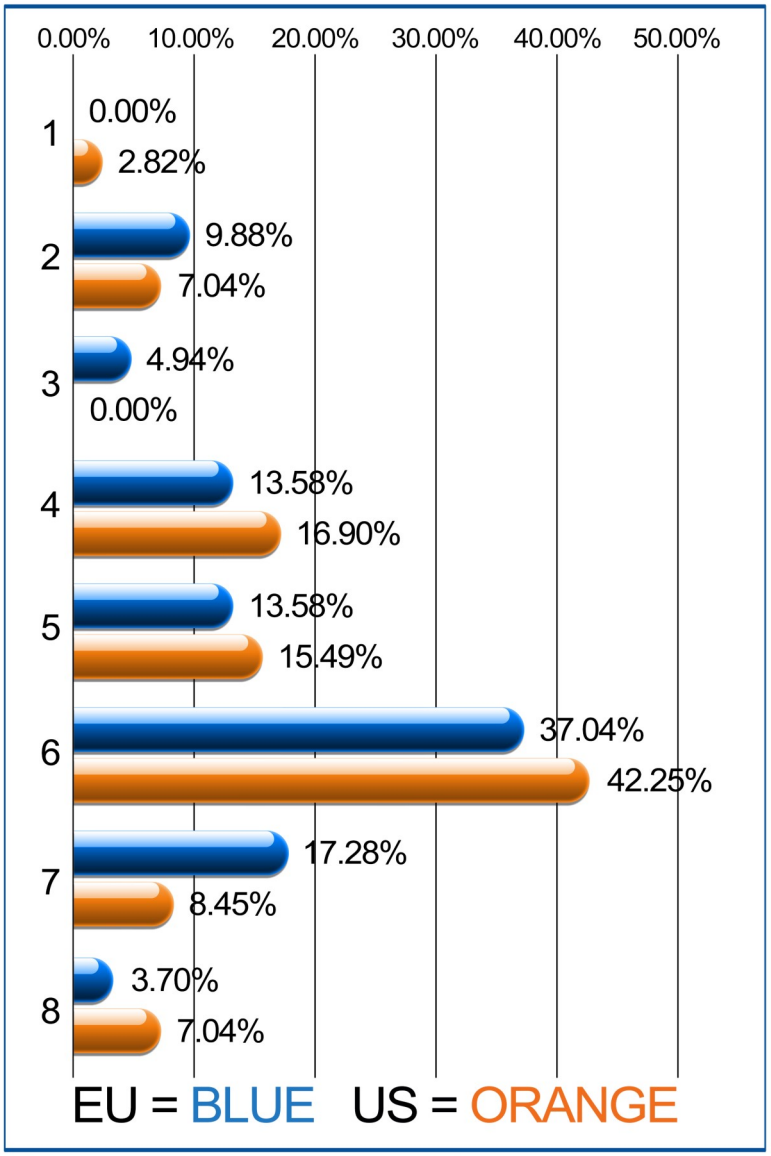
European responses = 85
United States responses = 82

#2 Where are bioassays developed

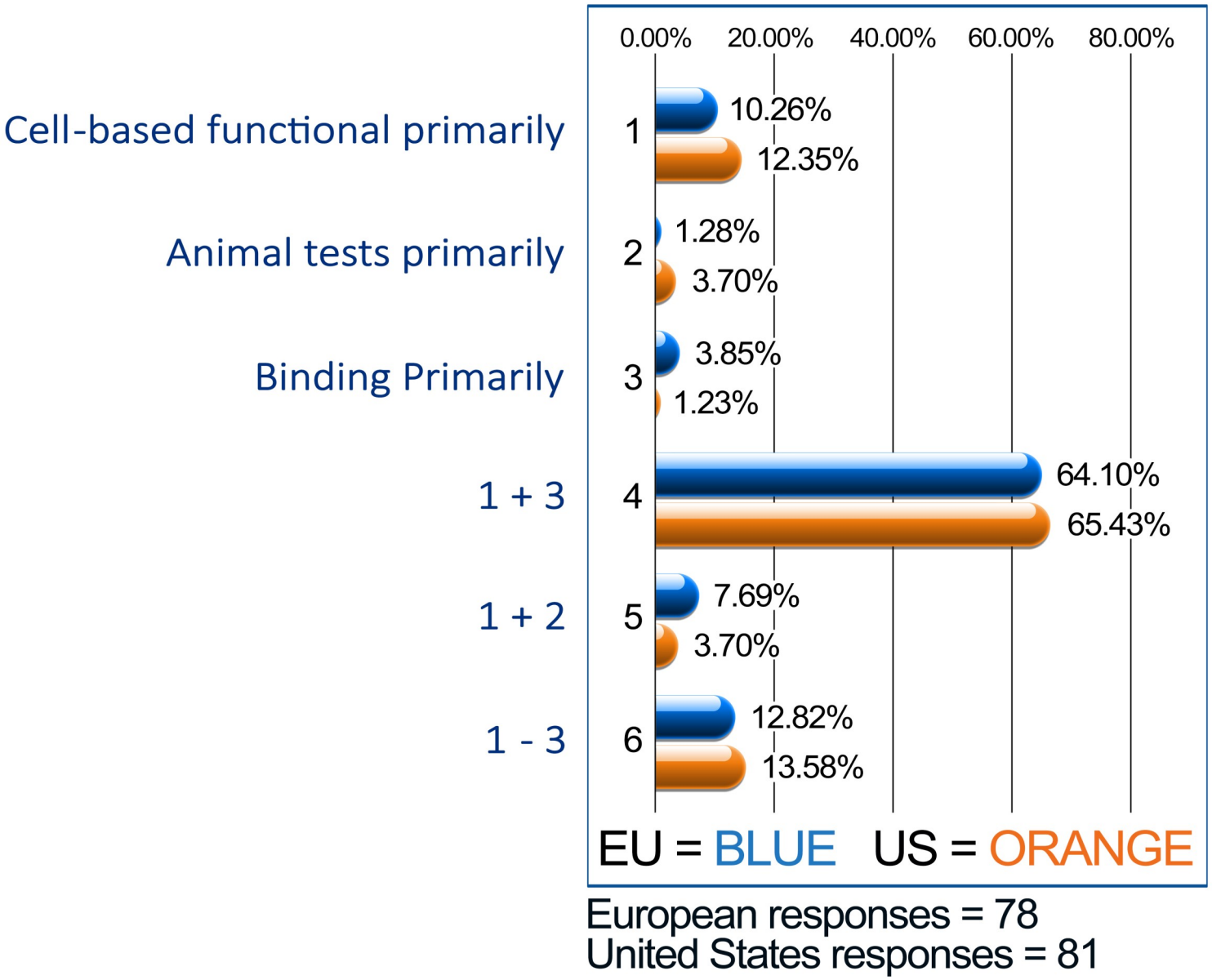


European responses = 78
United States responses = 86

Stages at which assay(s) used

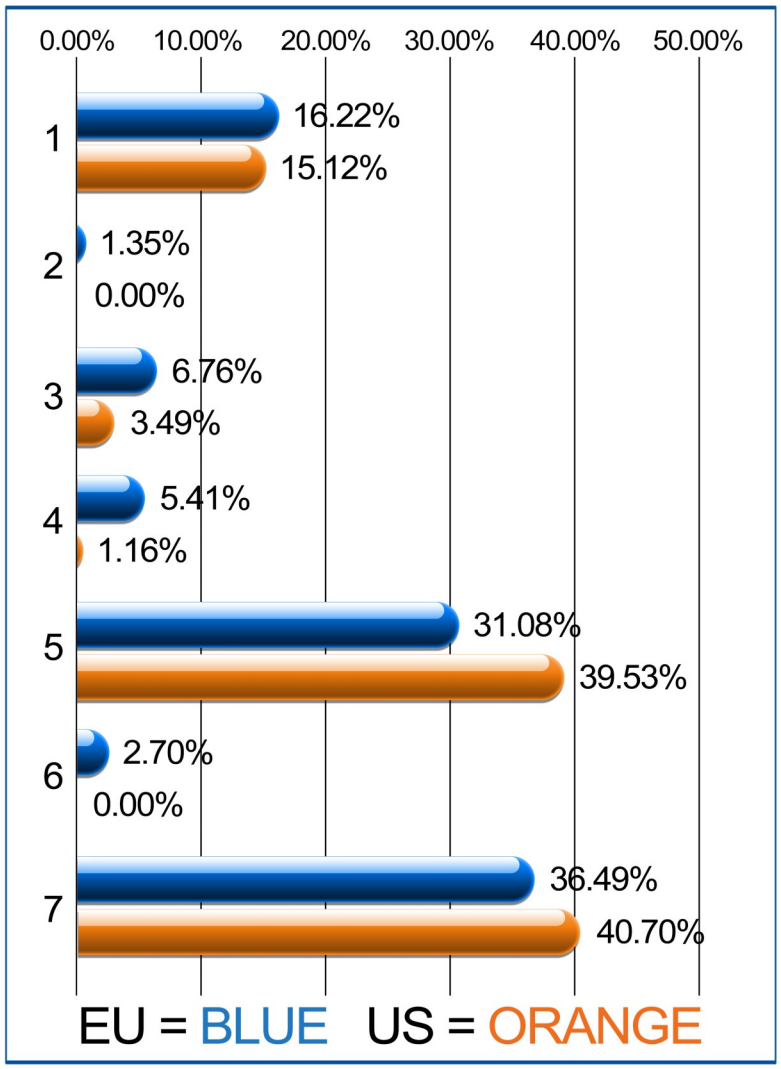


European responses = 81
United States responses = 71



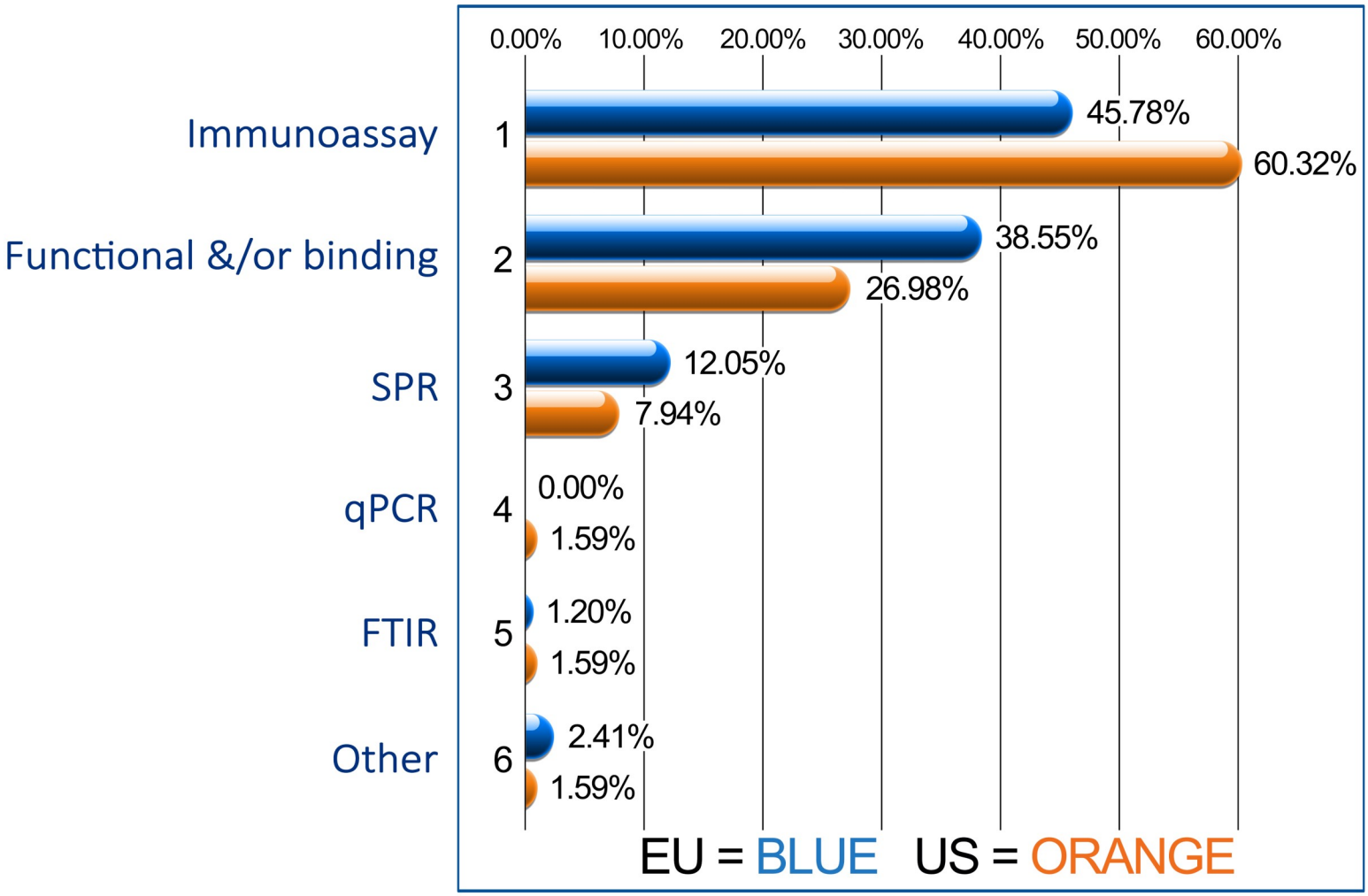
European responses = 78
United States responses = 81

Which functional assay types used?



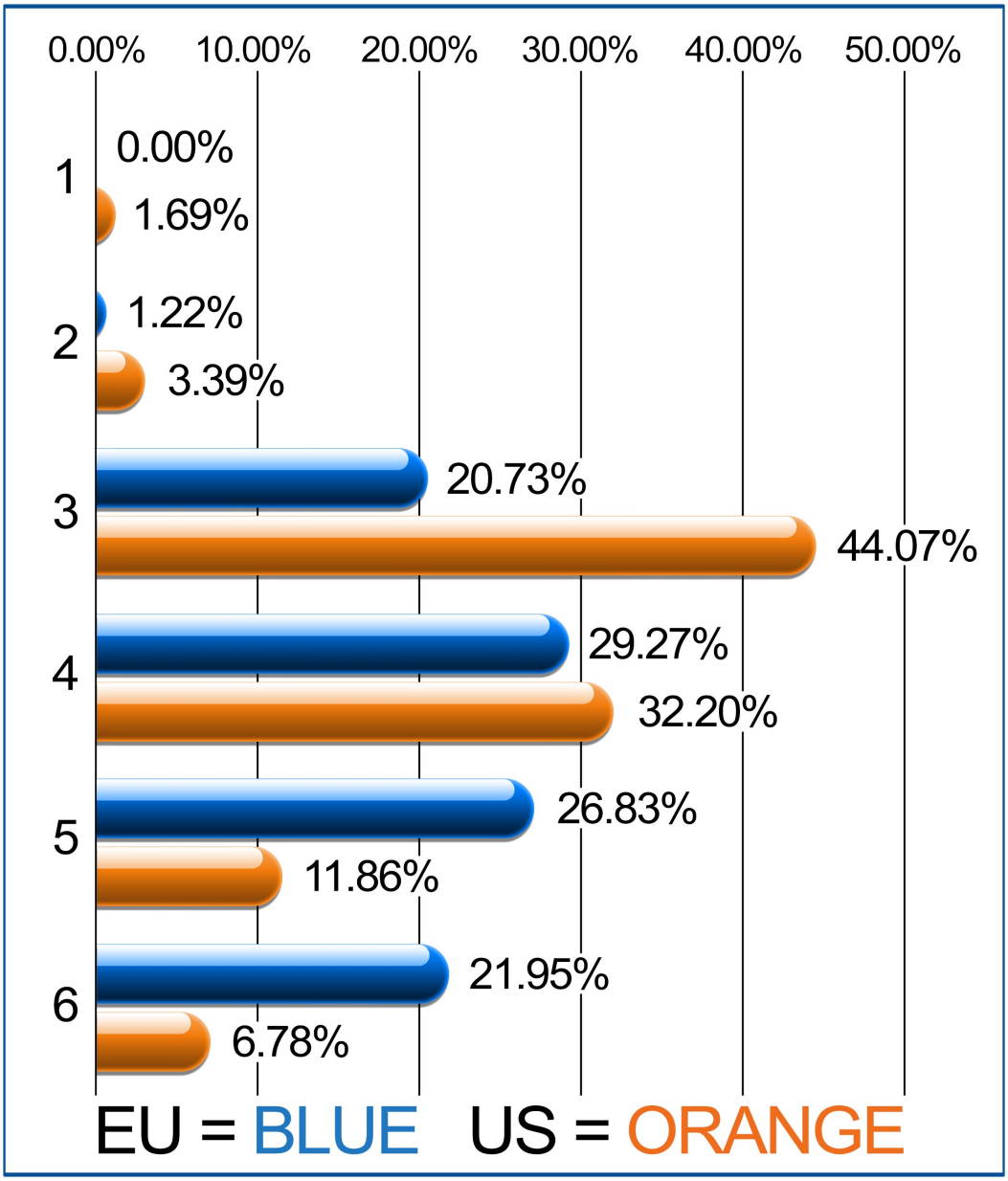
European responses = 74
United States responses = 86

Binding assay type (primarily)



European responses = 83
United States responses = 63

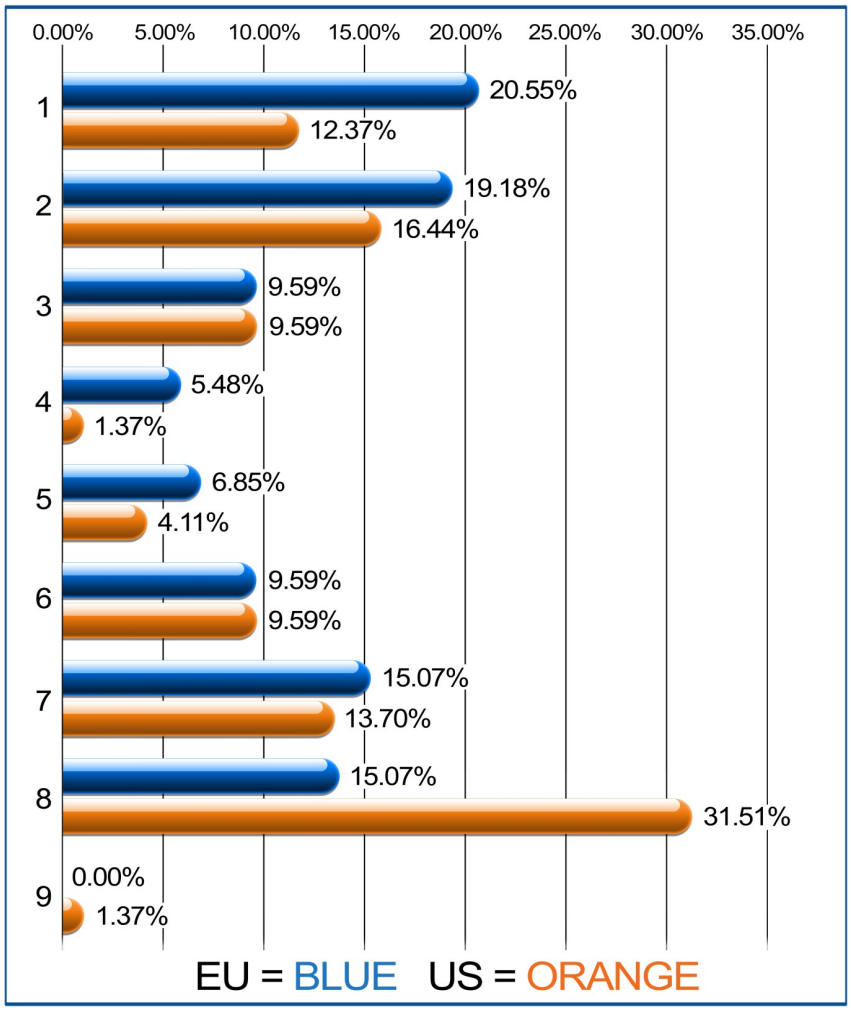
How many bioassay systems do you run?



European responses = 82
United States responses = 59

#8

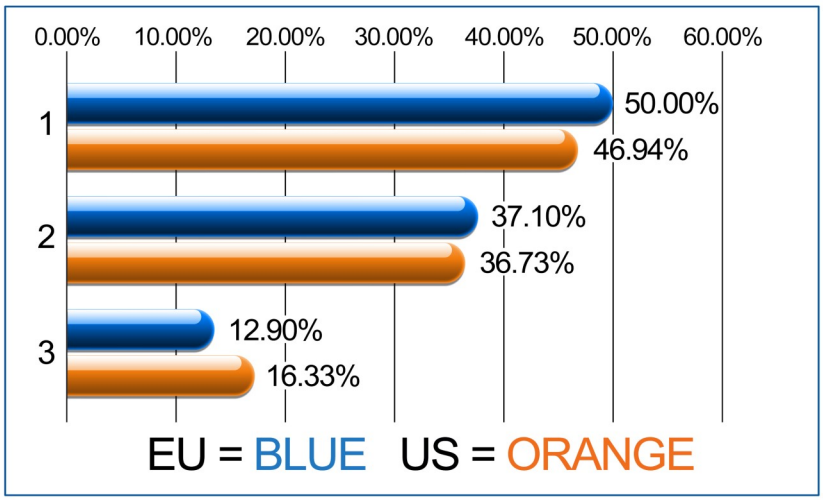
What is your current use of DOE?



European responses = 73
United States responses = 73

#9

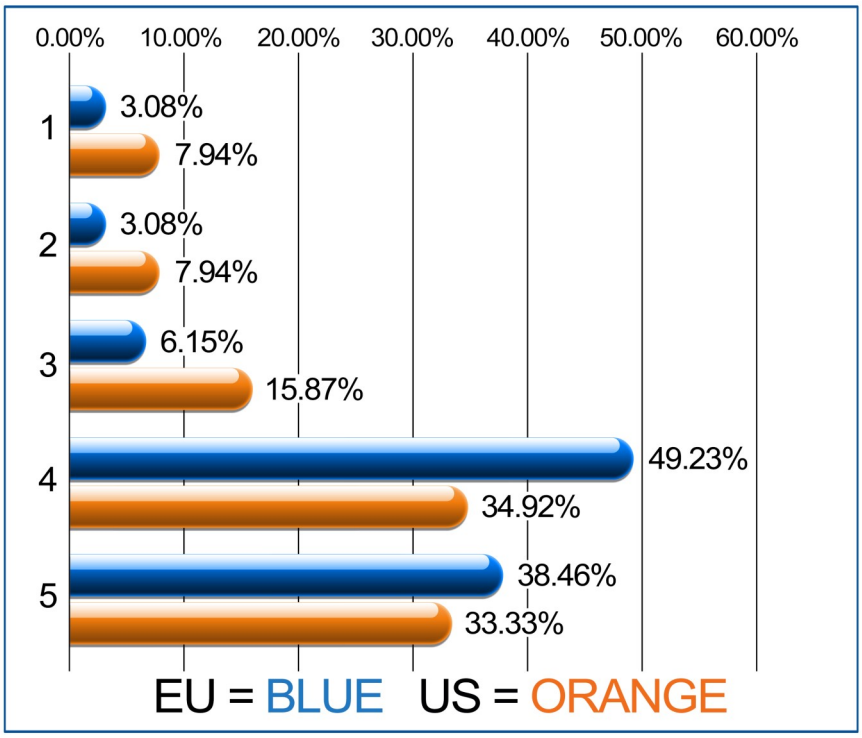
How do you design your DOEs?



European responses = 62
United States responses = 49

#10

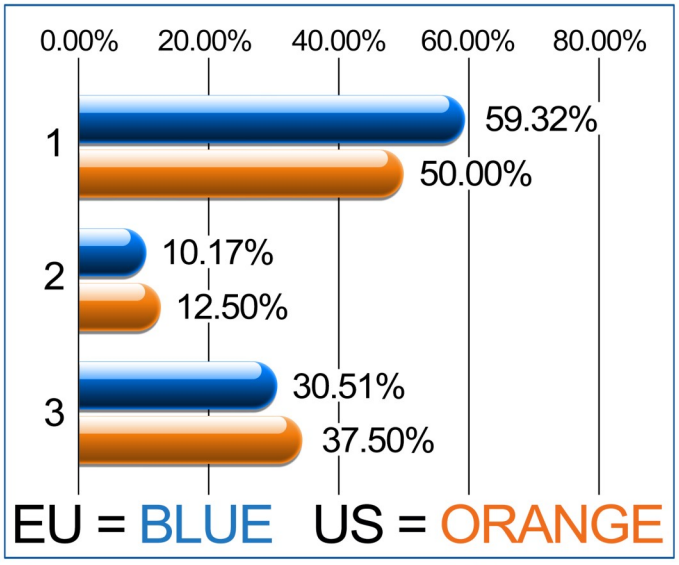
What type of DOE designs do you use?



European responses = 62
United States responses = 49

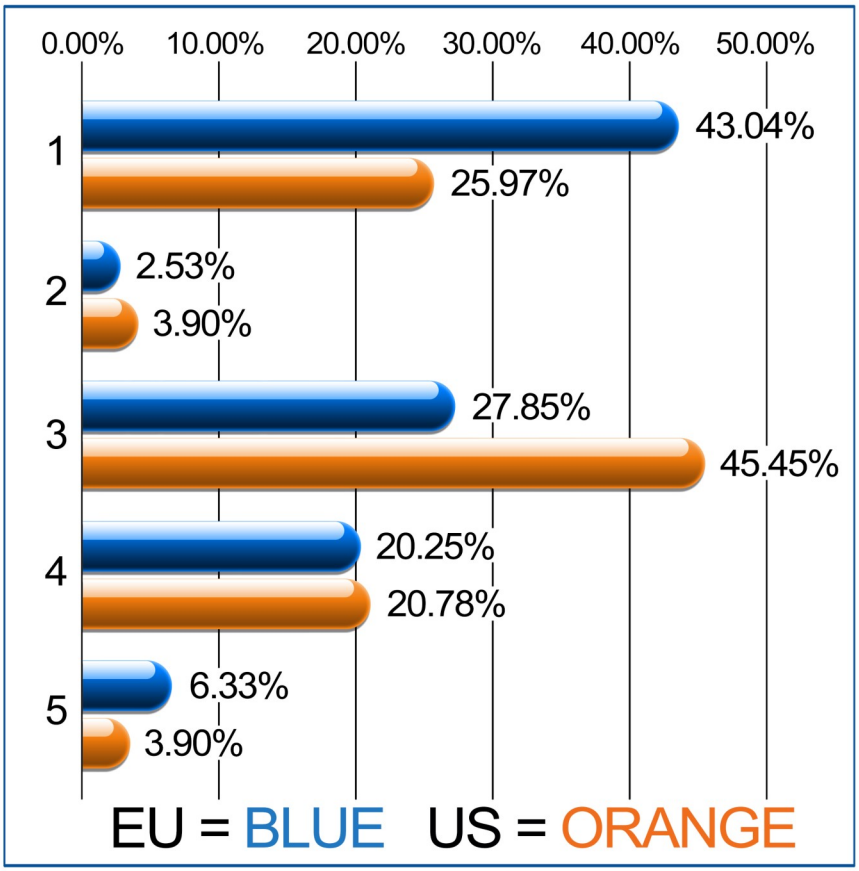
#11

Concerning cell-based assays using multi-well plates: do you optimize well-to-well characteristics of your plates?



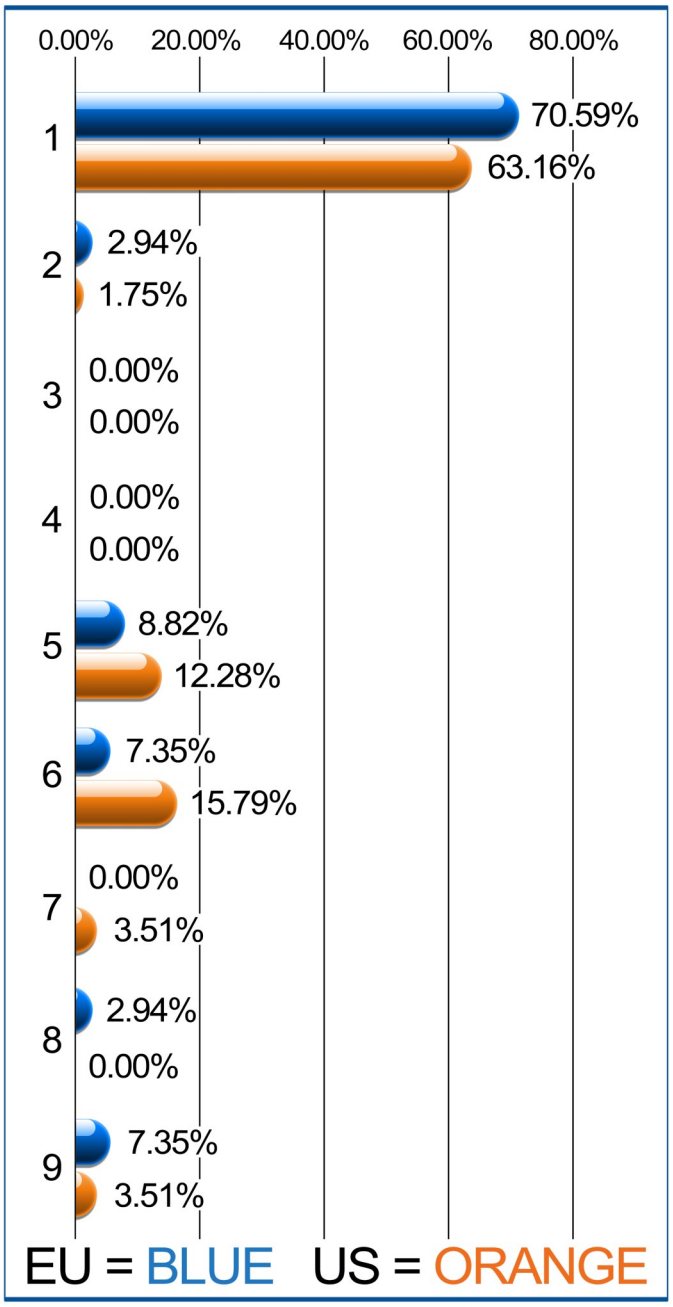
European responses = 59
United States responses = 48

Do you use "ready-to-use cells"?



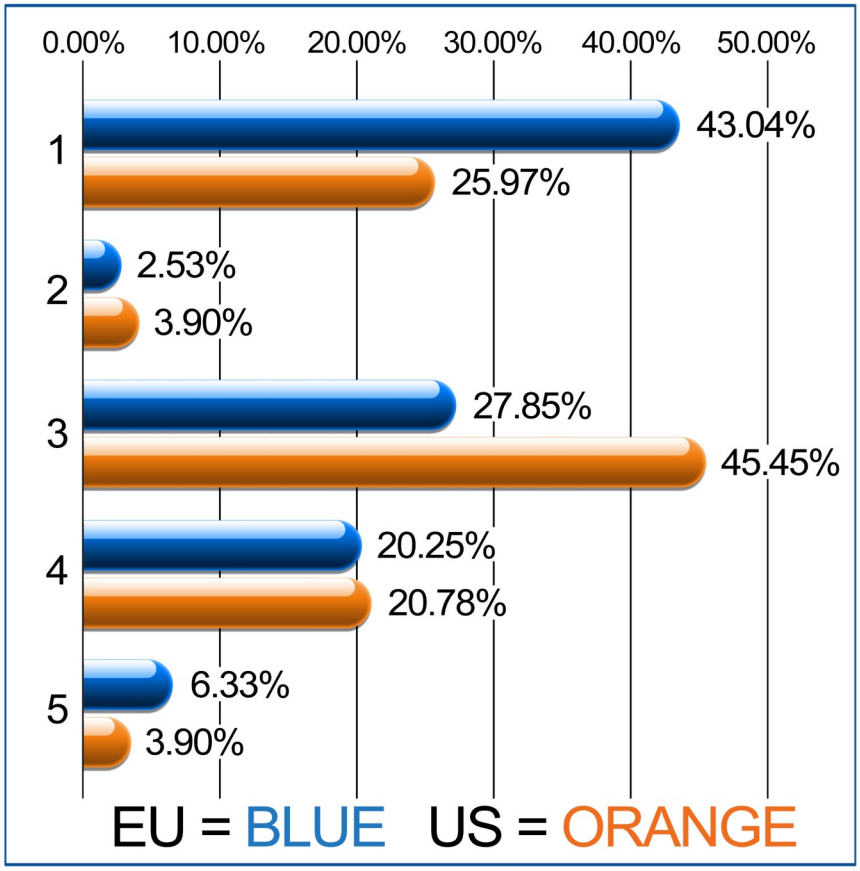
European responses = 79
United States responses = 77

Have you had any discussion on DOE with regulators?



European responses = 68
United States responses = 57

Do you use "ready-to-use cells"?



European responses = 79
United States responses = 77

Use of ready-to-use cells by different types of organization

	Contract		Small Biopharm < 50 employees		Mid Biopharm 50 – 300 employees		Global Biopharm		Consultant		Research Institute		Other	
	EUR	US	EUR	US	EUR	US	EUR	US	EUR	US	EUR	US	EUR	US
Total responses	**14**	**10**	**3**	**1**	**23**	**9**	**29**	**38**	**0**	**3**	**4**	**2**	**1**	**3**
Never	6	1	1	1	9	1	9	12			3	2	1	1
Always					1		1	2						
Whenever possible	4	7	2		8	4	8	14		3				1
Just implementing	4	2			4	4	8	8						
Not applicable					1		3	2			1			1

Note: the total responses shown in this table (74 for the EUR survey, 66 for the US) are fewer than the total responses given to the question 12 on use of ready-to-use cells (79 for EUR, 77 for US) because some respondents to the question did not state what type of organization they were

The majority of answers to Question 16 were received from contract organizations, mid-biopharm and global biopharm companies, in each of which the combination of "whenever possible" plus "just implementing" outweighed the answer "never" (Table 2). Noticeably, for contract organizations, the European survey showed 6 out of 14 responses as never using, compared with the US survey which showed only 1 out of 10 as never using ready-to-use cells. Similarly, for mid-biopharm the European survey showed 9 out of 23 responses never using while the US survey showed only 1 out of 9 as never using. However, for global biopharma, there was little difference between European survey, with 9 out of 29 (31%), and the US survey, with 12 out of 38 (32%), responses of never using ready-to-use cells.