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Review

A survey on IVIVC/IVIVR development in the pharmaceutical industry – Past experience and current perspectives

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ABSTRACT

The present work aimed to describe the current status of IVIVC/IVIVR development in the pharmaceutical industry, focusing on the use and perception of specific approaches as well as successful and failed case studies. Two questionnaires have been distributed to 13 EFPIA partners of the Oral Biopharmaceutics Tools Initiative and to the Pharmacokinetics Working Party of the European Medicines Agency in order to capture the perspectives and experiences of industry scientists and agency members, respectively. Responses from ten companies and three European Agencies were received between May 21st 2014 and January 19th 2016. The majority of the companies acknowledged the importance of IVIVC/IVIVR throughout the drug development stages and a well-balanced rate of return on investment. However, the IVIVC/IVIVR approach seemed to be underutilized in regulatory submissions. Four of the ten companies stated to have an internal guidance related to IVIVC/IVIVR modelling, whereas three felt that an overall strategy is not necessary. Successful models mainly served to support formulation development and to provide a better mechanistic understanding. There was not yet much experience with safe-space IVIVRs as well as the use of physiologically based modelling in the field of IVIVC. At the same time, the responses from both industry and agencies indicated that there might be a need for a regulatory framework to guide the application of these novel approaches. The relevance of IVIVC/IVIVR for oral IR drug products was recognized by most of the companies. For IR formulations, relationships other than Level A correlation were more common outcomes among the provided case studies, such as multiple Level C correlation or safe-space IVIVR, which could be successfully used for requesting regulatory flexibility. Compared to the responses from industry scientists, there was a trend towards a higher appreciation of the BCS among the regulators, but a less positive attitude towards the utility of non-compendial dissolution methods for establishing a successful IVIVC/IVIVR. The lack of appropriate *in vivo* data and regulatory uncertainty were considered the major difficulties in IVIVC/IVIVR

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development. The results of this survey provide unique insights into current IVIVC/IVIVR practices in the pharmaceutical industry. Pursuing an IVIVC/IVIVR should be generally encouraged, considering its high value from both industry and regulators' perspective.

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1. Introduction

Understanding the impact of changes of *in vitro* drug product characteristics on the *in vivo* performance is a key factor to successful drug development and ultimately plays a crucial role in all stages of a drug product's life cycle. To this end, a traditional *in vitro*/*in vivo* correlation (IVIVC) model describes the mathematical relationship between *in vitro* dissolution properties and *in vivo* pharmacokinetics of modified release (MR) products, typically divided into the correlation of whole curves (Level A), of summary parameters (Level B) and of single point(s) (Level C or multiple Level C) according to the United States' Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidelines (FDA, 1997; EMA, 2014). The concept has been extended to be utilized for immediate release (IR) dosage forms with different release rates as well (Ostrowski and Baczek, 2010). In contrast to IVIVC, *in vitro*/*in vivo* relationship (IVIVR) often referred to nonlinear approaches (Polli, 2000; Mendyk et al., 2015) and a Quality by Design framework (Dickinson et al., 2008; Opara and Legen, 2014; Sjogren et al., 2014). In this article, the term "IVIVR" is defined to cover any type of relationship between *in vitro* dissolution properties and *in vivo* performance that is not included in the classical IVIVC concept described above, *e.g.* Level D/rank order correlation. Thus, IVIVR also included cases where changes in *in vitro* dissolution properties do not impact *in vivo* pharmacokinetics, resulting in a dissolution 'safe space' in the present study. The safe-space specification is then set to ensure dissolution performance remains within the region where bioequivalence is assured, for example based on the slowest dissolution profile tested in the clinical study (Dickinson et al., 2008).

Successful development of an IVIVC/IVIVR leads to a number of benefits, helping *e.g.* to provide regulatory evidence for changes in scale-up and post-approval changes, to set dissolution specifications and to obtain biowaivers. However, there is currently a variety of gaps to be filled to obtain maximum benefit of IVIVCs/IVIVRs (Sjogren et al., 2014). In order to gain insights into the current status of IVIVC/IVIVR development in the pharmaceutical industry, a questionnaire has been developed and circulated to 13 medium to large pharmaceutical companies, EFPIA members of the Steering Committee of the Oral Biopharmaceutics Tools (OrBiTo) project funded by the Innovative Medicines Initiative (http://www.imi.europa.eu/content/orbito), on May 9th 2014. The goal was to collect information on IVIVC/IVIVR performance within the companies including approaches, benefits and difficulties, highlighting putative factors of success as well as differences between the companies with regard to strategies and commonly used methods.

In addition, a similar survey was developed to capture the regulators' perceptions and experiences with IVIVC/IVIVR in reviewed marketing authorisation applications (MAA). Capturing both industry and regulator perspectives was used to focus on essential shortcomings in order to improve the framework for IVIVC/IVIVR development in a manner which meets the needs of both industry and regulators and reduces the risk of dispensable *in vivo* studies as well as deficient MAA with regard to IVIVC/IVIVR.

2. Methods

The industry questionnaire consisted of four parts: Part 1 contained 17 general questions on benefits and difficulties, the companies' experience and success rate with IVIVC/IVIVR modelling as well as their

perspectives on specific approaches. Part 2 and 3 included almost the same questions on methods and data handling to be answered with respect to successful cases and failed attempts, respectively. Part 4 aimed to gather details on case examples in order to generate a database of past successes and failures with IVIVC/IVIVR modelling.

The second questionnaire was distributed to the members of the Pharmacokinetics Working Party through the European Medicines Agency office on October 26th 2015. This 'regulator survey' comprised two parts: Six questions covered the reviewer's perception and expectations of different aspects of IVIVC/IVIVR modelling, while the second part (five questions) referred to their experiences from the review of MAA containing IVIVC/IVIVR attempts.

In both questionnaires, IVIVR was expressly defined to include safe-space relationships as well. In many questions, the respondents were encouraged to select different answers for IVIVC and IVIVR, respectively. Definitions were also provided with regard to modelling approaches: The *one-stage method* was described as a *convolution-based approach*, where the relationship between *in vitro* release and plasma concentration was directly modelled using the convolution integral. In contrast, the *two-stage method* was denominated the *deconvolution-based approach*, which involves two steps: Firstly, the calculation of the *in vivo* absorption/dissolution profile *via* deconvolution, and secondly, the correlation of *in vivo* and *in vitro* dissolution data (Huhn and Langguth, 2013).

The validity of the questionnaires has been assessed by EFPIA members of the OrBiTo project as well as representatives from different medical product agencies.

During evaluation, a scoring strategy was introduced when a ranking was considered more informative than presenting the answers only. This was applicable if different statements/options to a specific aspect were provided with an estimate of frequency, given the possible answers "never", "rarely", "sometimes", "often" and "always". These answers were scored 1–5, with 1 for "never" or "not applicable", 2 for "rarely", 3 for "sometimes", 4 for "often" and 5 for "always". Multiplying the score with the number of respondents selecting this answer gave the sum of all scores for one statement/option. Dividing this sum of scores by the total number of respondents yielded the average score which allowed a ranking of different statements/options. In question eight, for example, five possible difficulties for introducing an IVIVC/IVIVR were listed, each to be related to an estimate of frequency by ticking "never"–"always" (Table 1). The average score for "regulatory uncertainty" was calculated as followed:

$$5 \times 1 + 4 \times 3 + 3 \times 5 + 2 \times 1 \text{ (one responded always, three often, five sometimes, one rarely)} = 5 + 12 + 15 + 2 = 34 \text{ (sum of scores)}$$

$$34/10 = 3.4 \text{ (average score for n} = 10 \text{ for part 1 and part 2 of the questionnaire)}$$

3. Results

3.1. The industry perspective

The completed parts 1–3 of the questionnaire were received between May 21st 2014 and February 17th 2015. The last case studies (part 4) were provided on September 1st 2015. The overall time frame to which the answers referred ranged from five to 20 years with a mean of 9.3 ± 5.1 years. Ten companies completed part 1 as well as 2 and six companies part 3 of the questionnaire. Among the three EFPIA partners of the OrBiTo project who did not take part in the survey, one representative stated that the IVIVC/IVIVR approach did not play any role in their company.

3.1.1. General aspects

Eight of the ten participating companies had profound experience in IVIVC/IVIVR modelling. The majority agreed that IVIVC/IVIVR saves money/resources (seven respondents agreed or strongly agreed, three were neutral) and developed the models in both early and late development (nine both, one late development only). The percentages of IVIVC/IVIVR attempts with regard to the overall drug product portfolio and success rates were variable (Fig. 1).

Regulatory and non-regulatory benefits as well as challenges in IVIVC/IVIVR development are listed in Table 1. Notably, seven of the

Table 1
Benefits and difficulties of introducing and developing IVIVC/IVIVR.

Applications (n = 10)		Difficulties (n = 10)		Reasons for failure (n = 6)	
Option	Score*	Option	Score*	Option	Score*
For better mechanistic understanding of potential clinical impact of changes in formulation and manufacturing process	3.7	Lack of appropriate clinical data	3.4	Model does not meet the validation criteria	3.7
To support formulation development	3.7	Regulatory uncertainty	3.4	Lack of appropriate clinical data	2.8
To set dissolution specifications for drug products	3.0	Deficiency in time and resources	3.3	Deficiency in time and resources	2.7
To support Quality by Design	2.7	Inapplicable compound properties	3.0	No difference in the *in vitro* release characteristics	2.3
To obtain biowaiver	2.5	Complexity of required dissolution method	3.0	Complexity of required dissolution method	2.0
–	–	Inability to meet regulatory thresholds for external/internal predictability	2.8	Additional comments: - Complex release mechanism - Transporter-mediated absorption - Correlation was not found	–
–	–	Inapplicable formulation properties including limitations in producing formulations with modified release rates (slow and/or fast)	2.8	–	–
–	–	Lack of appropriate dissolution method	2.8	–	–
–	–	Uncertainty in general return on investment	2.8	–	–
–	–	Lack of appropriate model/modelling skills	2.4	–	–

* This is the average score, calculated by dividing the sum of scores by the number of respondents (1 - never, 2 - rarely, 3 - sometimes, 4 - often, 5 - always).

ten respondents confirmed that the dissolution specifications based on IVIVC/IVIVR were at least sometimes wider than the normal ± 10% range, while their experience with the regulatory acceptance of this outcome reflected mixed feelings (one responded often, four sometimes, one rarely, one never, three selected no answer). Four respondents felt that there is a need for a regulatory framework to guide the use of forms of IVIVR other than the classical IVIVC and six shared this opinion with regard to the use of novel approaches, *e.g.* PBPK modelling.

In general, the safe-space concept does not seem to be well-established as supporting clinical examples are scarce (two responded high, five low, one none and two not applicable). Two companies stated that they do not use safe-space results to request regulatory flexibility at all.

The majority of the companies preferred to evaluate the models using results from past experiments over the course of drug development rather than only based on studies specifically planned for establishing an IVIVC/IVIVR (Fig. 2). Interestingly, there was not always a general strategy in place. Three respondents stated that an overall strategy was not necessary and that decisions to initiate the development of an IVIVC/IVIVR were made case-specifically. Four companies declared to have an overall strategy or an internal guidance. Regardless of the presence of an overall strategy, the majority of the companies primarily developed the models proactively, *i.e.*, in anticipation of requesting regulatory flexibility, instead of reactively, *i.e.*, triggered by regulatory questions on dissolution specifications or batch variability (Fig. 2).

3.1.2. Compound and formulation properties

Half of the respondents rarely or never developed IVIVC/IVIVR models with non-oral dosage forms (Table 2). On the other hand, at least half of the respondents also put a focus on IVIVC/IVIVR models with oral IR formulations (Table 2). The respondents were also asked to specify the number of successful IVIVC/IVIVR cases in the last 10 years, categorized by BCS class and formulation type. Two respondents answered often, one sometimes and for three companies, the percentage of successful models with IR products related to the sum of successful cases from all categories was calculated to be 69%, 86% and 89%, respectively.

The current industry perspective on the impact of the BCS class in pursuing an IVIVC/IVIVR is non-uniform (Fig. 3). Six of the ten respondents at least sometimes used the BCS to assess the feasibility of an IVIVC/IVIVR for IR formulations. Five companies agreed that the BCS is an adequate system for this purpose. Among the five respondents who (strongly) disagreed with this statement, three at least sometimes applied an alternate classification system and two rarely used any system (BCS or alternate).

3.1.3. Dissolution testing

Four of the ten companies often or always used two different dissolution methods: one for quality control and another for formulation development with focus on IVIVC/IVIVR, respectively. The majority of the respondents often used non-pharmacopeial dissolution media, *e.g.* FaSSIF, when pursuing an IVIVC/IVIVR, whereas alternate dissolution setups such as the Artificial Stomach-Duodenum model or the TNO Gastro-Intestinal Model (TIM) were much less often employed (Fig. 4A). Five and six of the ten respondents acknowledged the importance of alternate dissolution methods and media, respectively, to facilitate IVIVC/IVIVR development (Fig. 4B).

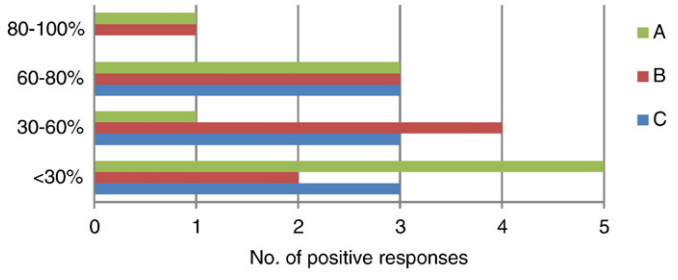

Fig. 1. Incidence and success rate of IVIVC/IVIVR attempts; green: percentage of IVIVC/IVIVR attempts *versus* overall portfolio of drug products in filing, red: success rate according to internal evaluation, blue: success rate according to regulator's acceptance of model for application requested.

3.1.4. In vivo data

Compounds with high *in vivo* variability were stated to be subject to IVIVC/IVIVR attempts by at least four companies, but with a rather low rate of success: Only one respondent declared that the number of successful IVIVC/IVIVR with highly variable drugs at their company were high, seven answered low and one very low.

Three respondents reported that they did not pursue an IVIVC/IVIVR with drugs where pharmacokinetics studies could not be performed in healthy volunteers and one did not have any experience in this field. The remaining seven companies mostly favored the use of biorelevant dissolution testing (one replied always, one often, four sometimes) and *in silico* absorption modelling (three responded often, three sometimes) in such cases. FaSSIF/FeSSIF and TIM-1 were mentioned twice in this context. At least half of the respondents also recognized the use of animal data for this type of compound (two replied often, three sometimes, three rarely, two never) and in IVIVC/IVIVR development in general – only three companies did not use animal data for establishing IVIVCs/IVIVRs at all. Animal data were mostly used as exploratory tool and predominantly in development, not commonly in approval (Fig. 2).

In vivo data for establishing an IVIVC/IVIVR were typically gained from cross-over studies conducted in the fasted state (Table 3). Half of the respondents felt that it is necessary to use data obtained under fasting conditions for developing an IVIVC/IVIVR. Six of the ten companies often favored the use of cross-study data. In contrast, the number of studies with a parallel design and adaptive study designs were limited (Table 3). Four companies usually assessed, reported and evaluated differences between the populations used for internal and external validation. Notably, the study populations were hardly tested for *in vivo* factors that could affect drug dissolution, *e.g.* gastrointestinal pH, transit times and mechanical forces in most of the companies (Fig. 2).

3.1.5. IVIVC/IVIVR modelling and model validation

Among the 10 participating companies, the primarily used technique to establish an IVIVC/IVIVR was the two-stage method, while only few respondents recognized the use of the one-stage method and population pharmacokinetics (Table 3). As expected, linear models clearly outnumbered non-linear ones. Table 3 shows some common approaches of data handling/manipulation along with the calculated average scores. Nine of the ten respondents (strongly) agreed that introducing a lag time and/or time scaling factors facilitates the development of a successful IVIVC/IVIVR, whereas only five shared the same perception of the correction for flip-flop kinetics. Analyzing the individual responses, mean *in vivo* data were more often used than individual ones for establishing IVIVCs/IVIVRs for four companies, equally often for two and less often for the remaining four companies.

Four of the ten companies always assessed both internal and external predictability of the model. One company claimed to use internal validation only. The remaining 50% performed internal and/or external validation as needed.

Only half of the respondents confirmed that they often applied *in silico* simulations to support IVIVC/IVIVR development (three replied sometimes, two never). Among the 14 case studies provided by five companies, *in silico* simulations were applied in four cases, *e.g.* to justify wider dissolution limits (Table 4).

3.1.6. Types of correlation and regulatory submission

The frequency of the levels which were developed decreased with A > C > > D (rank order correlation) > B (Table 2). Two companies

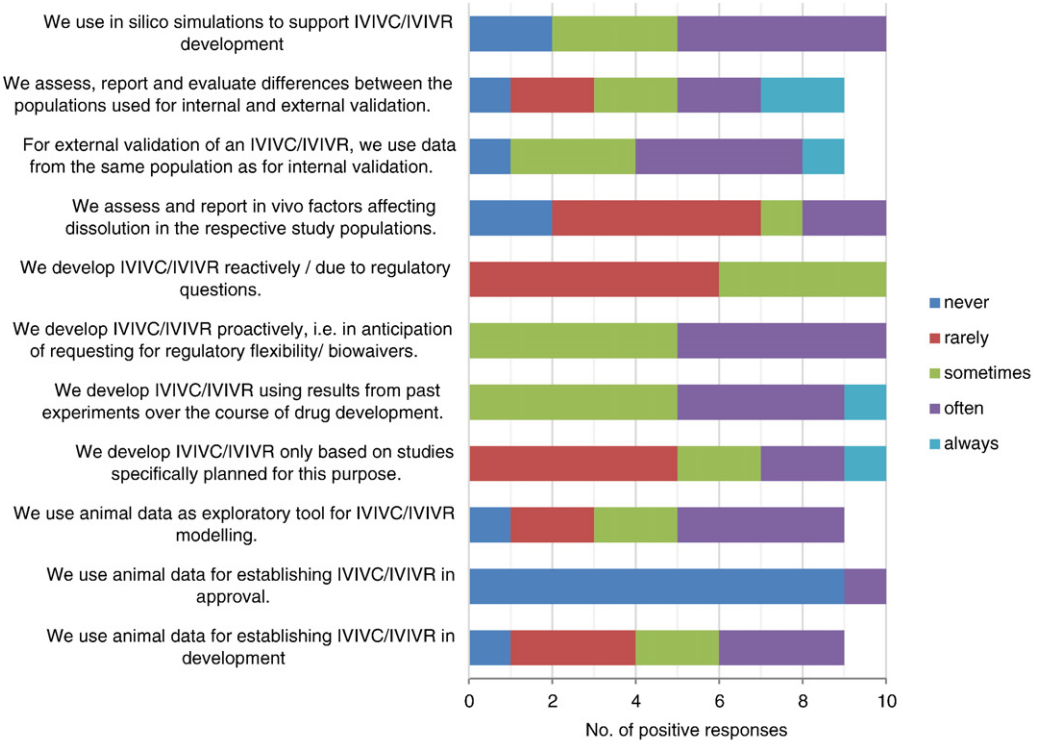

Fig. 2. Concepts and strategies.

(strongly) agreed that it is necessary to have only Level A correlations in filing. On the other hand, five respondents (strongly) disagreed with this statement and three were neither pro nor contra. Accordingly, five of the ten companies sometimes or often had other than Level A correlations in regulatory submissions (one responded rarely, three never).

3.1.7. Failures

Table 1 contains common reasons for failed IVIVC/IVIVR attempts with the corresponding average scores, calculated based on responses from six companies. In an attempt to identify putative factors of success, the answers to similar questions of part 2 (with respect to successful cases only) and part 3 (with respect to failed attempts only) have been compared for the individual companies. Interestingly, the success rate seemed to be independent of the applied strategy, the use of pre-clinical data and alternate computational methods or certain modelling techniques. As the most pronounced discrepancy, alternate dissolution media and fasted state data were more often used in successful cases compared to failed attempts in three out of six companies.

3.2. An overview of case studies

Using part 4 of the questionnaire, detailed information on 14 IVIVC/IVIVR cases has been received from five companies, performed with variants of eight IR and six MR formulations (Table 4). These case studies covered small molecules of all BCS classes with molecular weights of 120–520 (750 for one prodrug) including two basic, nine acidic and three neutral drugs. Six compounds were subject to active transport, eight to metabolic enzymes and three to both.

Table 2
Types of formulation and correlation[a].

	Never	Rarely	Sometimes	Often	Always
We develop IVIVC/IVIVR with non-oral formulations.	4	1	3	2	0
We develop IVIVC/IVIVR with oral IR products.	0	3	2	5	0
We develop Level A IVIVCs.	1	2	3	1	3
We develop Level B IVIVCs.	5	4	1	0	0
We develop Level C IVIVCs.	3	3	1	3	0
We develop Level D IVIVCs.	4	4	1	1	0

[a] Figures correspond to number of positive responses based on 10 respondents.

The specified dissolution methods were mostly simple and developed to support both IVIVC/IVIVR development and quality control (Table 4). In all but one case, the paddle apparatus (USP II) was employed. The selected dissolution media were all compendial ones, but IR products (Table 4, No. 01–08) tended to require more intricate approaches than MR products.

Cross-over studies in healthy volunteers were clearly predominant (Table 4). Interestingly, two projects involving drug administration in the fed state resulted in a successful Level A and multiple Level C correlation, respectively (No. 01 and 14).

Additional information on the clinical studies used to establish the model revealed different approaches among the case studies. Primary and secondary goals were specified to be the assessment of drug-drug interaction, safety and tolerability, dose projection to phase 3, relative bioavailability and bioequivalence, among others. Notably, IVIVC/IVIVR models could be successfully established with two highly variable drugs ($n = 36$ and $n = 43$) and four moderately variable ones ($n = 12–48$).

The number of formulations investigated varied between the projects (two to ten variants) and IVIVC/IVIVR models with IR formulations tended to employ to a higher number of variants (three examples with four variants, one with 10 variants). The deconvolution technique was applied in all six cases involving MR products, using IR formulations (three examples), oral solutions (two examples) or a combination of both (one example) as reference formulations. Among the eight case studies involving IR formulations, standard bioequivalence evaluation was performed in four cases (safe-space IVIVR), ANOVA in one case (safe-space IVIVR) and linear regression in two cases (multiple Level C correlation). In one project (No. 03), a linear Level A correlation was successfully established using a one-stage differential-equation based approach as described by Buchwald (2003).

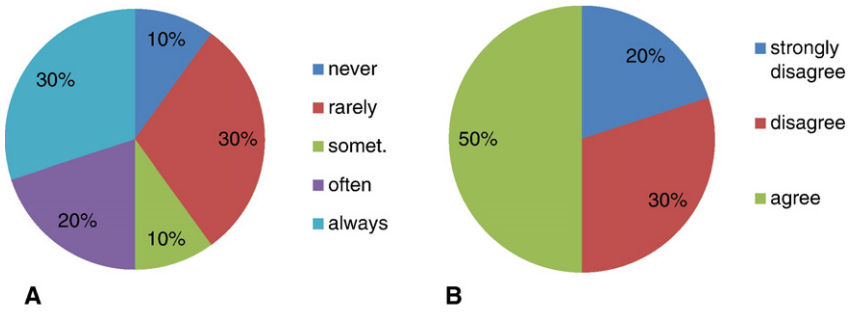

Fig. 3. Applicability of the Biopharmaceutics Classification System (BCS) in IVIVC/IVIVR development; A: BCS used to assess the feasibility of an IVIVC/IVIVR for IR formulations, B: The BCS is an adequate system to assess the feasibility of an IVIVC/IVIVR for IR formulations.

The difficulties encountered during IVIVC/IVIVR development were specified for 8 out of the 14 provided case studies (Table 4). Most of the challenges were attributed to regulatory concerns (four examples) or to the *in vivo* data (three examples).

3.3. The regulators' perspective

Three members of three European Agencies shared their thoughts and experience with the IVIVC/IVIVR approach in MAAs by participating in a survey containing 11 questions.

All respondents agreed that IVIVC is useful to promote process/formulation changes which would usually require an *in vivo* bioavailability study and to develop better mechanistic understanding of potential clinical impact of changes in the formulation and manufacturing process. Its value in setting dissolution specifications and supporting QbD development were recognized by two of the three respondents. These answers roughly correspond to the frequency of potential applications of IVIVC from the industry perspective (Table 1) and to the experience of the FDA as outlined in a PQRI workshop report (Van Buskirk et al., 2014). All respondents specified the percentage of IVIVC/IVIVR attempts with regard to all reviewed MAAs during the past 10–15 years to be lower than 30% for both oral MR and IR products as well as non-oral products, except for one agency member who observed a medium frequency (30–60%) of IVIVC attempts with oral MR products in MAAs. There was no consistent agreement on whether IVIVCs are more often seen in recent submissions than five years ago (one agreed, one disagreed, one remained neutral).

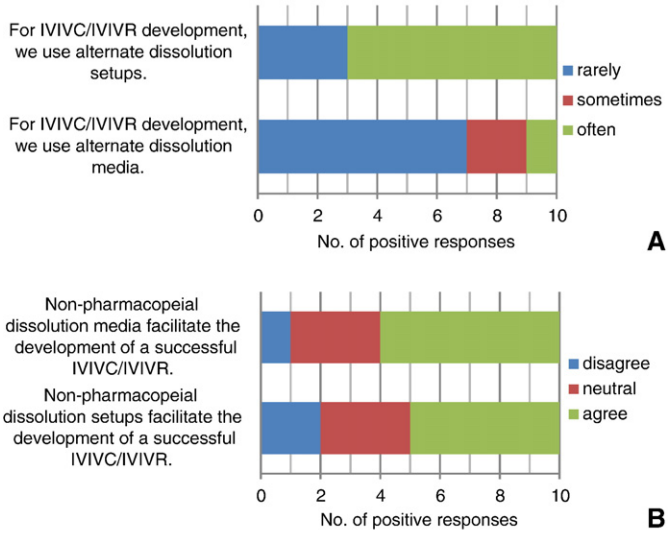

Fig. 4. Use of alternate dissolution methods and media in IVIVC/IVIVR development (A: frequency, B: perspective).

While none of the agency members agreed that IVIVC/IVIVR should be pursued with all compounds irrespective of the BCS class, their perception of the IVIVC/IVIVR approach with particular types of compound and formulation differed. All respondents expected to see IVIVC attempted for MR products, but only one expressed the same expectation of IR formulations with BCS class 2 or 4 compounds. The BCS was considered an adequate system to evaluate the likelihood of a successful IVIVC for IR products by two of three assessors.

Two respondents rarely and one never have seen sponsors using alternate computational methods for establishing IVIVC/IVIVR. There seemed to be no regulatory consensus as to whether alternate computational methods including PBPK modelling facilitate the development of a successful IVIVC/IVIVR (one agreed, one was neutral, one provided no answer). Two of the three agency members confirmed that further regulatory guidance on the use of novel approaches is needed.

For compounds where pharmacokinetic studies in healthy volunteers cannot be performed, one respondent would sometimes consider *in silico* simulations and animal data, the other two rarely or never, respectively. According to the comments, two agency members would endorse pharmacokinetic studies in patients in such circumstances, while one does not believe that IVIVCs/IVIVRs can be developed without studies in healthy volunteers at all.

Only one agency member acknowledged the use of non-pharmacopeial dissolution media for developing a successful IVIVC/IVIVR. Two of the three respondents stated that sponsors often tended to propose the same dissolution test that was used in establishing IVIVC/IVIVR for routine quality control. These two agency members also sometimes or often observed dissolution specifications based on IVIVC/IVIVR which were wider than the normal $\pm 10\%$ range, but would not generally approve them, even if they are supported by the *in vivo* data.

For establishing IVIVC, all respondents considered the cross-over study in the fasted state to be the ideal study design. This notwithstanding, they would also accept data from studies with parallel design and would not generally disapprove of data obtained under fed conditions. Their perspective on adaptive study designs were less consistent (one was positive, one neutral and one provided no answer). Regarding the utilization of cross-study data, the agency members were either irresolute (two remained neutral) or skeptical (one would not be in favor of such data).

The variable extent of submitted IVIVC/IVIVR documentation is the major challenge according to one agency member. They explained the varying degree of documentation by the fact that the available guidance is not very detailed regarding the required documentation. Another respondent expressed their skepticism about safe-space IVIVRs as they believe that the absence of a correlation rather indicates that dissolution was not predictive of the bioavailability. In their opinion, setting a safe space is only possible when there is a relationship between dissolution and bioavailability. The other two agency members stated that there is a need for a regulatory framework to guide the use of safe-space IVIVR in Quality by Design and for setting clinically relevant specifications.

Table 3
Study designs, modelling approaches and data handling.

Study design		Techniques/models		Data handling	
Option	Score*	Option	Score*	Option	Score*
Cross-over design	4.0	Two-stage method	3.8	Mean *in vitro* data	4.3
Only fasted state	3.8	Compartmental modelling	3.0	Lag time correction/time scaling	3.8
Cross-study data	3.1	PBPK modelling	2.9	Individual *in vivo* data	3.4
Parallel design	2.0	Linear models	2.8	Mean *in vivo* data	3.2
Adaptive design	1.8	One-stage method	2.4	Correction for flip-flop kinetics	2.6
–	–	Non-linear models	1.8	Individual *in vitro* data	1.9
–	–	Population pharmacokinetics	1.7	–	–

* This is the average score, calculated by dividing the sum of scores by the number of respondents (1 - never, 2 - rarely, 3 - sometimes, 4 - often, 5 - always).

4. Discussion

4.1. The industry perspective

In the authors' view, the responses underline the importance of IVIVC/IVIVR throughout the drug development stages and point to the interdisciplinary efforts behind it, but also a well-balanced rate of return on investment. Fotaki et al. (2013) reported similar trends based on a survey with 57 responses received from June 29th 2011 to July 24th 2011. It should be noted, however, that the web-based survey by Fotaki and coworkers aimed at scientists across academia, industry and regulatory agencies at the same time and a strict definition of IVIVC was not provided beforehand. In comparison, our survey addressed a smaller group ($n = 13$) of innovator companies and included more detailed questions on the use and perception of specific approaches as well as successful and failed case studies. It should be kept in mind that the number of respondents was limited ($n = 10$ for part 1 and 2, $n = 6$ for part 3) and their answers may have been affected by the companies' OrBiTo membership.

4.1.1. General aspects

Differentiating the reported success rate with regard to internal evaluation and the regulators' acceptance of the model for the application requested, respectively, the “internal success rate” was higher in five companies. This is not surprising since the “internal success” could be associated with other applications of the model, *e.g.* for dosage form selection or evaluation of formulation and process robustness. Successful IVIVC/IVIVR models, indeed, more often served to provide better mechanistic understanding of potential clinical impact of changes in formulation and manufacturing process and to support formulation development than to set dissolution specifications or to obtain a biowaiver (Table 1). These responses suggest that the return on investment of an IVIVC/IVIVR model was not only confined to the regulators' acceptance.

The prevalent strategy to develop the models in a proactive way rather than to wait for the regulatory trigger (Fig. 2) was, from the authors' perspective, testament to the general awareness of the opportunities of a successful IVIVC/IVIVR model, but also to the experts' sensibility to start IVIVC/IVIVR considerations before it was inevitable to.

According to the calculated average score, the lack of appropriate clinical study data, regulatory uncertainties and deficiencies in time/resources were the main difficulties in IVIVC/IVIVR development (Table 1). The following paragraphs delve into various stages of IVIVC/IVIVR, focusing on the issues that may be encountered at each step and the industry perception and experience with successful cases in this respect.

4.1.2. Compound and formulation properties

The responses indicate that IVIVC/IVIVR with oral IR drug products plays a role for the majority of the companies (Table 2, Table 4, see also Section 4.2). Compared to IVIVC with MR formulations, attempts with IR drug products require extended decision making steps beforehand. The most prominent approach to identify compounds with dissolution and/or permeation as the rate-limiting step for absorption was launched by Amidon and coworkers as the Biopharmaceutics Classification System (BCS) >20 years ago (Amidon et al., 1995). Apparently, there is not yet any other classification system which is about to replace the BCS completely, but the original BCS is no longer considered adequate neither (Fig. 3). In order to fill this gap, some companies developed their own decision-supporting tools as part of a formulation finding strategy based on in-house and literature data (Branchu et al., 2007; Mackie et al., 2012; Muenster et al., 2016). An alternative interpretation could be that a strict classification system for IVIVC/IVIVR development may not be absolutely necessary. It is possible that the IVIVC/IVIVR approach could be applicable to compounds crossing BCS barriers as evident by the response from the five companies that sometimes or rarely applied a classification system.

4.1.3. Dissolution testing

Table 1 shows that the lack of an appropriate dissolution method was to a lesser extent an issue than the complexity of the required dissolution method. Justifying the utilization of a complex dissolution method may become an issue associated with a deficiency in time and resources which ranked second on the list of difficulties stated by the companies (Table 1). Furthermore, high complexity of the required dissolution method precludes its application for quality control. Compendial dissolution setups such as the USP II apparatus and simple buffers were most probably the approach of choice for six of the ten companies who at least sometimes strived for a two-in-one solution. For the four companies who did not confirm the value of non-compendial dissolution testing to faciliate IVIVC/IVIVR development (Fig. 4B), alternate setups/media were probably not yet considered truly superior to compendial methods based on their cost-benefit analysis. The infrequent use of non-pharmacopeial setups (Fig. 4A) might partly be due to the relatively high investment required and the relatively low throughput of these models compared to standard dissolution apparatus.

4.1.4. In vivo data

Inadequate or missing *in vivo* data was the primary challenge for the majority of the companies (Table 1) which may be traced back to different issues addressed in the questionnaire.

Firstly, particular features of the drug itself may necessitate enhanced efforts in the pharmacokinetic assessment. This holds true for compounds with high *in vivo* variability, for example, for which seven companies reported low success rates when pursuing an IVIVC/IVIVR. Another complex category included drugs where pharmacokinetic studies in healthy volunteers could not be performed, *e.g.* genotoxics, as two respondents stated that they did not develop IVIVC/IVIVR models with these drugs at all.

Secondly, data integrity can be influenced by the type of data framework and the data volume that the IVIVC/IVIVR model relies on. Since the companies mostly preferred to evaluate the model using results from past experiments over the course of drug development (Fig. 2), an optimized methodology may help to make full use of all *in vivo* data collected up to the current study. Cook (2012) suggested a

Table 4
Overview of case studies.

No.	BCS class	Do-sage form	Out-come	Dissolution method	For QC	Clinical study	Stage of development	IVIVC approach	Filing	Difficulties	Applications
01	4	IR tablet	Multiple Level C	USP II, 50 rpm, pH 6.8 PB with 0.1% SLS, 5 TP within 60 min, T80% <5–20 min	Yes	Crossover, 12 HV, fed (standard breakfast), moderate VAR, 4 formulations	Late	Linear regression, no simulations, mean data	Yes	n/a	Better mechanistic understanding of clinical impact; support formulation development
02	2	IR coated tablet	Multiple Level C, linear	USP II, 60 rpm, water with 0.6% SDS, 1000 ml, 4 TP within 120 min	Yes	6 studies, crossover, 12–20 HV, fasted, approx. 20% RSD for Cmax and AUC, 10 formulations	Phase 3	Linear regression, mean data, %PE, internal and external validation	Yes	Level A not achieved for all formulations	Support formulation development, justification of specifications, multiple Level C accepted for biowaiver
03	4	IR tablet	Level A, linear	USP II, 50 rpm, pH 2 → 5 → 6.4 → 7.4 → 8.2, each pH condition for 30 min followed by buffering to the next pH, 10 TP within 150 min, T80% 35–90 min	No	3 studies incl. 2 for validation, crossover, 43 HV, fasted, approx. 50% RSD for Cmax and AUC, 4 variants + capsule RF	Transfer to late phase (dose projection for phase 3)	Simulation in parallel, mean data, time scaling and use of representative conc.-time profile, internal and external validation	No, IVIVC used internally	Conventional dissolution incl. 2-step methods failed, Tmax VAR resulted in mean profiles which did not represent the observed Cmax-values	Support formulation development for commercial formulation, accelerate development timelines
04	2	IR tablet	Safe space	USP II, 100 rpm, 0.2% SDS, 13 TP within 120 min, T80% 20–<75 min, aqueous buffers also tested but reduced discrimination	Yes	Incomplete block design, 15 HV, fasted, low VAR, 3 variants + 2 RF (oral solution & standard IR tablet)	Late	Comparison according to standard BE criteria, no simulations	Yes	One Authority challenged the use of surfactant containing dissolution media, pushed instead for a (less discriminatory) simple aqueous buffer	Better mechanistic understanding of clinical impact; set dissolution specifications; support QbD; support formulation development
05	4	IR tablet	Safe space	USP II, 50 rpm, 0.2% Tween 80, 12 TP within 60 min, T80% 15–>60 min, 3 other surfactant media & FaSSIF also tested	Yes	Crossover, 24 HV, fasted, low VAR, 3 variants + 2 RF (oral solution & standard IR tablet)	Late	Comparison according to standard BE criteria, no simulations	Yes	For specification setting agencies wanted batch history/process capability taken into account as well as the *in vivo* data.	Better mechanistic understanding of clinical impact; provide regulatory evidence for SUPAC; set dissolution specifications; support QbD
06	4	IR tablet	Safe space	USP II, pH 6.0 buffer, 6 TP within 60 min, T80% <20–< 60 min, pH range 1.4–7.8 also tested	Yes	Incomplete block crossover, 20 HV, fasted, low VAR, 4 variants +2 RF (oral solution & standard IR tablet)	Late	ANOVA, no simulations	Yes	One authority asked for standard BE analysis of data.	Better mechanistic understanding of clinical impact; provide regulatory evidence for SUPAC; set dissolution specifications; support QbD
07	4	IR tablet	Safe space	USP II, 75 rpm, pH 7.4 buffer, 3 TP within 45 min, T80% <	Yes	Crossover, part of DDI study, 28 HV, fasted, moderate	Late	Standard BE criteria, no simulations	Yes	No	Better mechanistic understanding of clinical

				15–<45 min, 0.1 N HCl also tested		VAR, 2 variants + 1 RF (standard IR tablet)					impact; set dissolution specifications
08	4	IR tablet	Project stopped	USP II,75 rpm, pH 7.1 buffer, 3 TP within 60 min, pH shift also tested	To be developed	Adaptive design, 3-way crossover with optional 4th arm following interim readout, 16 HV, fasted, low VAR, 2 variants + 1 RF (standard IR tablet)	Phase 2	Standard BE evaluation, project stopped before further IVIVC evaluation could be performed	Project stopped before filing	n/a	Better mechanistic understanding of clinical impact; set dissolution specifications; support formulation development
09	1	MR, multi-particulate in capsules	Level A not achieved	USP II, 75 rpm, 0.05 M pH 6.0 PB, 500 ml, 3 TP within 24 h, T80% 16 h	–	Crossover, HV, 2 variants + 1 RF (IR)	Early	Linear regression, convolution, deconvolution, mean data, correction for lag time	No	Lack of appropriate clinical data → IVIVC unsuccessful as only mean clinical data available	Support formulation development
10	1	MR, fixed-dose combination	Multiple Level C - Level A not achieved	USP II, 75 rpm, pH 6.8 buffer, 11 TP within 24 h, T80% 8 h	Yes	Crossover, 36 HV, fasted, high VAR, 3 variants + 1 RF (IR)	Late	Linear regression, deconvolution/convolution, no simulations, mean data for Level C, individual/mean data for Level A	Yes	Level A challenging for highly variable, highly metabolized compound; differences in responses between agencies	–
11	1	MR	Level A, linear	USP II, 50 rpm, 0.02 M acetate buffer pH 4.5, 900 ml, 16 TP within 16 h, T80% 5–16 h	Yes	Crossover, HV, fasted, low VAR, 3 variants + 2 RF (oral solution & IR formulation)	Late	Two-stage method, individual data, correction for lag time	Yes	n/a	Obtain biowaiver, support formulation development
12	1	MR, coated tablet	Level A, non-linear	USP II, 50 rpm, 0.05 M PB pH 6.8, 1000 ml, 7 TP within 8 h, T80% 105–350 min	Yes	3 studies incl. 2 for validation, crossover, 27 HV, fasted (and fed, not used for IVIVC), 17–34% RSD for Cmax and AUC, 3 variants + 1 RF (oral solution)	Transfer to late phase	Two-stage method (numerical deconvolution), mean data, time scaling, simulations in parallel, internal & external validation	No, IVIVC used internally	Non-linear timescale-scale	Support formulation development, accelerate development timelines
13	1	MR, osmotic tablet	Level A, non-linear	USP VII, 30 cpm, 0.0825 N HCl + 2 mg/ml NaCl solution, 50 ml, 12 TP within 24 h	–	Crossover, 78 HV, fasted, intra-subject VAR ~35%, 3 variants + 1 RF (oral solution)	Late	Two-stage method, nonlinear regression, individual data, time scaling, 21 subjects used for external validation, use of simulations to justify wider specifications	Yes	n/a	Set wider dissolution specifications
14	3	MR, matrix tablet	Level A, non-linear	USP II, 100 rpm, 0.9% NaCl solution, 900 ml, T80% 4–24 h	Yes	Crossover, HV, high-fat meal, low-medium VAR, 2 variants, data for RF (IR formulation) obtained from different study	Late	Two-stage method (numerical deconvolution), individual data from MR tablet, mean data from IR, non-linear regression, use of simulations	Yes	Yes	Set dissolution specifications

AUC: area under the plasma concentration-time curve; Cmax: maximum plasma concentration; HV: healthy volunteers; IR: immediate release; MR: modified release; n/a: not available; PB: phosphate buffer; QbD: quality by design; QC: quality control; RF: reference formulation; RSD: relative standard deviation; SDS: sodium dodecyl sulfate; SLS: sodium lauryl sulfate; SUPAC: scale-up and post-approval changes; Tmax: time to maximum plasma concentration; TP: sampling time points; T80%: time to dissolve 80% of label claim; VAR: variability.

Bayesian approach in order to account for prior information when interpreting the result of an IVIVC study. Looking at our survey results, this approach did not yet seem to be fully established in practice. Depending on the purpose of the model, the time point to start IVIVC/IVIVR considerations may vary. Modi and coworkers, for instance, demonstrated a scheme for developing IVIVCs using data from *in vivo* studies that represented a typical development program of a controlled-release dosage form (Modi et al., 2000). To maximize the efficiency of any methodology, it may be advantageous not to wait until the first bioavailability/bioequivalence study in humans becomes available, but to start the discussion as early as possible based upon preclinical data, for example, to initiate training of an *in silico* model built to assess whether dissolution is likely to control oral absorption.

Thirdly, the clinical study design definitely has to be carefully considered. The most commonly applied study design (cross-over study in the fasted state) corresponds to the recommended study design for IVIVC studies according to the current regulatory guidelines (FDA, 1997; EMA, 2015) and the recently published experts' opinion (Van Buskirk et al., 2014). Although dosing the drug under fasting conditions is preferred for most drugs, it should be emphasized that poorly soluble lipophilic drugs are hardly absorbed in the fasted state. Hence, IVIVC studies in the fed state may be necessary to reflect drug product performance under clinical conditions (see successful IVIVCs in Table 4, No. 01 and 14). Investigating *in vivo* factors that could affect drug dissolution, *e.g.* gastrointestinal pH, transit times and mechanical forces, in the respective study populations might be valuable for drug products with complex pharmacokinetics and/or high *in vivo* variability as physiological variability may significantly affect the IVIVC/IVIVR in such cases. Furthermore, the use of the same population for external and internal validation did not appear to be the standard approach for half of the respondents (Fig. 2) and discrepancies between the populations used for external and internal validation may confound the overall outcome.

4.1.5. IVIVC/IVIVR modelling and model validation

Since the modelling work is usually not a straightforward process (Cardot and Davit, 2012), two questions addressed the common tricks and traps of data manipulation when performing mathematical IVIVC. Indeed, time scaling was applied in three cases and correction for lag time in two out of the 14 reported case studies (Table 4). While time scaling and lag time correction appeared to be well-known approaches, half of the respondents hardly had any experience with the correction for flip-flop kinetics (Table 3). Clearly, the scientific rationale, not solely mathematical reasons, should be provided if a lag time or scaling factors need to be introduced (Limberg and Potthast, 2013).

Averaging *in vitro* data seems to be a common practice for most of the companies (Table 3) and is not likely to have a significant impact on the model, as accurately explained by Cardot and Davit (2012). In contrast, performing the deconvolution step using the average plasma concentration–time curves is not recommended by the authorities (EMA, 2015). In practice, mean-based and individual-based IVIVC/IVIVR modelling appeared to be balanced (Table 3). Although there are case studies which demonstrated similar results for both techniques (Cardot and Davit, 2012), averaging the dataset implies a loss of important information and represents one of the most common reasons for IVIVC rejection at the FDA (Van Buskirk et al., 2014).

The majority of the respondents did not consider the lack of an appropriate model or modelling skills to be a major issue in their company (Table 1). This may be associated with the tacit understanding that if adequate *in vitro* and *in vivo* data as well as sufficient time and resources are available, the current tools usually allow the experts to establish a meaningful relationship or correlation. Meeting the regulatory thresholds for external/internal predictability appears to be more challenging in the end (Table 1). The survey results pointed to a heterogeneous picture of the industry experience in this respect, since less than half of the participating companies usually assessed both internal and external predictability of the model, as encouraged by the latest EMA guideline (EMA, 2015) and for narrow therapeutic index drugs, among others, by the FDA '*Guidance for Industry*' on IVIVC (FDA, 1997).

Modelling and simulation can be of great value when compound and formulation properties are to be evaluated with respect to the feasibility of an IVIVC/IVIVR, but also to support and guide IVIVC/IVIVR development in general. *Appendix III* of the new *'Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms'* released by the EMA contains descriptions of how (physiologically based) pharmacokinetic modelling can be used to assist in different steps during IVIVC development, *e.g.* to select the appropriate reference formulation or to make decisions on sampling times (EMA, 2015). Looking at the past performance (Fig. 2, Table 4), it appears that there is still opportunity for the companies to take more advantage of the use of PBPK modelling to support IVIVC/IVIVR development, taking into account the scientific as well as regulatory acceptance of physiologically based modelling approaches (Jiang et al., 2011; Van Buskirk et al., 2014; EMA, 2015) and the anticipated advances in this field (Kostewicz et al., 2014a).

4.1.6. Types of correlation and regulatory submission

Our survey results pointed to an inconsistent industry perception of the role of Level A correlations which is in line with the survey results reported by Fotaki et al. (2013). Although Level A correlations are preferred by the agencies, multiple Level C correlations are also considered valuable (FDA, 1997) or at least supportive in setting specifications (EMA, 2014). This attitude propagated to the industry performance such that the frequency of the levels which were developed decreased with A > C > > D (rank order correlation) > B (Table 2). The relevance of (multiple) Level C correlations appeared to be less recognized than expected by the authors, although there is a clear relation to Level A correlations: A successful multiple Level C correlation may serve as a basis for developing a Level A model and taking another perspective, if one fails to establish a Level A correlation, multiple Level C might still be achieved instead. In fact, a well validated Level A is not necessarily a prerequisite for achieving the most common benefits of IVIVC/IVIVR development (Table 1, Table 4, see also Section 4.2).

4.1.7. Failures

Regardless of the target level, the primary reason for failure was the inability of the model to meet the validation criteria, followed by the lack of appropriate clinical data and deficiencies in time and resources (Table 1). In contrast, *in vitro* issues less often played a role. It should be noted that only six of the 10 respondents who filled out part 1 and 2 of the questionnaire also completed part 3 which referred to failed attempts. This could indicate that failed cases may not be as systematically recorded as successful ones.

The observed absence of any relationship between a company's success rate in IVIVC/IVIVR modelling and the use of specific tools, techniques and strategies should be interpreted with care, since this industry insight involved a wide range of compound and formulation types with diverse demands and challenges. The quality of the applied tools, *e.g.* the *in silico* model or the preclinical studies, may also confound the result of any comparative evaluation. Taking the low response rate to part 3 and the heterogeneity of the companies' portfolio into account, the trend towards a more frequent use of alternate dissolution media and fasted state data in successful cases compared to failed attempts could be reevaluated using a predefined set of compounds and formulations for a better confirmation.

4.2. An overview of case studies

Given the inherent heterogeneity, the provided case studies (Table 4) could be used to start an IVIVC/IVIVR database to be maintained beyond the OrBiTo project, allowing for *e.g.* mapping compound spaces over which particular *in vitro*, *in vivo* and *in silico* approaches are most promising for developing IVIVC/IVIVR. For the moment being,

this small database can be considered a selected overview of past performances in IVIVC/IVIVR development in the pharmaceutical industry.

Although IVIVCs with IR formulations have been reported to be much less frequently pursued compared to MR products (Van Buskirk et al., 2014), the answers provided in part 2 and the case studies collected in part 4 of our survey point out that their role should not be underestimated in future discussions on IVIVC. Interestingly, four of the eight examples which involve IR products were described to be successful safe-space IVIVRs. This high percentage of safe-space IVIVRs is probably not representative of the current IVIVC/IVIVR portfolio, considering the limited number of clinical examples supporting the safe-space concept (see Section 3.1.1). Nevertheless, these various outcomes of IVIVC/IVIVR development with IR formulations indicate that a Level A correlation might not always be achievable, but other forms of relationship which could still be beneficial for both regulatory and non-regulatory purposes. The mechanistic background of this observation has been elaborated elsewhere (Polli et al., 1996; Dickinson et al., 2008). Notably, all of the provided safe-space examples were used in regulatory submissions (Table 4). This positive experience contradicts the answers of two respondents who stated that safe-space results were not used to request regulatory flexibility at all. In the authors' view, a less conservative perception of IVIVC may elevate the chance of IVIVC projects to be initiated and successfully accomplished. This also holds true for the definition of success in IVIVC development. Although reducing the regulatory burden might be the ultimate goal of IVIVC development in most companies, a model that strictly meets the regulatory thresholds is not absolutely necessary for achieving the two main applications of successful IVIVC/IVIVR models (Table 1). This was well reflected by four case studies where the results were not filed, but still associated with benefits in formulation development (Table 4). Taking only regulatory purposes into consideration, the level of correlation to be used in filing might be another subject of debate according to the answers, as four of the ten companies rarely or never used other than Level A in filing and two felt that it is necessary to have a Level A IVIVC for filing (see also Section 3.1.6 and 4.1.6). This opinion was not supported by the provided case studies: All three multiple Level C correlations were used in regulatory submissions, whereas two of the five successful Level A correlations were not. Remarkably, a multiple Level C correlation was accepted for a biowaiver, after Level A had been shown to fail for the same formulations. Thus, the case studies presented here suggest a more flexible perspective of evaluating the success or return on investment of IVIVC/IVIVR models and that correlations other than level A could be applied in regulatory submissions.

The described dissolution methods show that finding an adequate dissolution protocol for IR products might sometimes be more challenging than for MR products, but in most cases, acceptable discriminatory power could be achieved with simple setups and media. Biorelevant media was only mentioned in one of the 14 projects as one of the conditions that was tested but finally not selected for establishing the IVIVC model. A possible explanation could be that dissolution testing with biorelevant media was not standard practice in the past. Nonetheless, there are many efforts being made, *e.g.* within the OrBiTo project, in order to establish a "toolkit" of release tests adaptable to formulation peculiarities (Kostewicz et al., 2014b), suggesting an enhanced use of alternate dissolution methods in the future.

The information on the *in vivo* studies performed to develop the IVIVC/IVIVR model (Table 4) was in line with the statistics gained from the general questions of part 1 and 2 (Table 3), confirming that the cross-over study under fasting conditions was the predominant study design in IVIVC/IVIVR development. Considering fasted state conditions as the "gold standard" in this field (FDA, 1997; EMA, 2015), the examples where data obtained after meal intake were employed for establishing an IVIVC (Table 4, No. 01 and 14) demonstrate that there may be exceptions from the rule. Interestingly, these models were also successfully used in the regulatory submissions in order to set dissolution specifications and to support formulation development, respectively.

The four case studies where the primary goals of the clinical study were stated to be other than pursuing an IVIVC highlighted the variety of *in vivo* investigations on drug product performance/characteristics that IVIVC/IVIVR studies could be embedded in. Hence discussions on introducing an IVIVC/IVIVR in early phases would minimize the number of required studies and subjects as well as maximize the output with regard to multiple objectives. The fact that gastrointestinal physiological parameters have not been assessed in any of the projects might be considered a drawback with regard to the mechanistic understanding of *in vivo* formulation behavior and its variability.

The IVIVC modelling approaches with MR formulations (Table 4, No. 09–14) were in agreement with the recommendations of the regulatory guideline (EMA, 2015), whereas those with IR dosage forms were more heterogeneous (Table 4, No. 01–08). The variety of approaches was probably due to the lack of guidance and technical challenges in this field (Ostrowski and Baczek, 2010).

The most prominent difficulties among the case studies presented in Table 4, *i.e.*, regulatory concerns (No. 04–06 and 10) and inadequate or missing *in vivo* data (No. 02, 09 and 10), are in accordance with the major issues that were deduced from the general statistics (Table 1) and discussed in the previous Sections (4.1.1 and 4.1.6). It should be noted that regulatory concerns, based on questions raised by the regulators (Table 4), and uncertainties, associated with putative regulatory issues that are expected from the industry's perspective, are not necessarily the same. In practice, these uncertainties possibly go along with other problems which are not only related to purely regulatory aspects. Assessing the reported regulatory challenges helped to get an impression where these uncertainties probably originate from. Apart from scientific aspects in research and development as indicated by some case examples, regulatory issues might also be traced back to different interpretations of the existing guidance and the lack of timely discussions/consultancy in early stages of IVIVC/IVIVR development. It remains the company's individual strategy to define and overcome these difficulties. In summary, particular efforts should be put into starting both internal and external dialogues in order to reduce regulatory uncertainties and deficiencies in the generation and/or collection of clinical data for IVIVC/IVIVR development.

4.3. The regulators' perspective

The regulators' perspective discussed here were limited to three agency members only and, due to the survey's questions, mostly restricted to the clinical pharmacokinetics viewpoint. Nevertheless, this questionnaire represents the first step to start a dialogue addressing unmet needs of both sponsors and assessors with respect to IVIVC/IVIVR in MAA filing at the EMA.

The regulators' answers regarding the frequency of potential applications of IVIVC roughly corresponds to the responses given by industry scientists (Table 1) and to the experience of the FDA as outlined in a PQRI workshop report (Van Buskirk et al., 2014). The estimates of frequency of IVIVC/IVIVR attempts given by both assessors and industry members (Fig. 1) suggested that IVIVC/IVIVR is underutilized in regulatory submissions. This is in conflict with the positive opinion of both industry and regulators with respect to the significant benefits of successful IVIVC/IVIVR models.

Compared to the responses from the industry scientists, there appears to be a trend towards a higher appreciation of the BCS among the regulators (see also Fig. 3), but a less positive attitude towards IVIVC/IVIVR with IR products. The latter aspect is in accordance with the FDA experience, reporting a lower percentage and quality of IVIVCs filed for IR products (Van Buskirk et al., 2014). As pointed out in the previous Sections (4.1.2 and 4.2), the relevance of IVIVC/IVIVR with IR formulations should not be neglected. Therefore a comparative analysis of

the applied tools/approaches and/or interactive discussions between regulators and industry scientists are recommendable in order to accelerate improvements in this field.

The value of *in silico* simulations as a complementary tool to classification systems to assess the feasibility of an IVIVC/IVIVR with IR products should be systematically investigated, since there seems to be no generally accepted best practice with regard to this issue. From the scientific literature, it is evident that novel approaches for building IVIVC models such as physiologically-based IVIVC (Kesisoglou et al., 2015; Mistry et al., 2016) are not yet fully validated. However, they offer alternatives if conventional methods fail and may substantiate, as needed, the importance of physiological parameters and their variability. Alternate computational methods are currently considered auxiliary tools by both regulators (EMA, 2015) and industry (Fig. 2, Table 4), but they are not yet well established in IVIVC/IVIVR development according to the results of both industry and regulator surveys. There are cumulative efforts from both industry and academia within the OrBiTo project to further validate and optimize the use of PBPK modelling in formulation development, focusing on the integration of dissolution data in PBPK models. Hence, enhanced utilization of *in silico* simulations, in particular PBPK modelling, may be expected in future IVIVC projects.

Another application of *in silico* simulations involves compounds where pharmacokinetic studies in healthy volunteers cannot be performed. According to the comments, two agency members would rather endorse pharmacokinetic studies in patients in such circumstances, while one does not believe that IVIVC/IVIVR can be developed without studies in healthy volunteers at all. This is contrary to the industry experience of the utility of biorelevant dissolution testing, animal data and *in silico* absorption modelling in this context (see Section 3.1.4). It should be noted that the regulators' answers referred solely to the IVIVC/IVIVR approach in approval, whereas the industry perspective includes the practicability during drug development as well. This might also partly explain the fact that the companies tend to acknowledge the usefulness of alternate dissolution setups and media for developing a successful IVIVC/IVIVR (Fig. 4) more than the regulators do. Another reason for two of the three respondents might be their prevailing experience with sponsors who tend to propose the same dissolution test that was used in establishing IVIVC/IVIVR for routine quality control. Interestingly, it has recently been reported that the FDA expects the IVIVC and quality dissolution test methods to be identical (Van Buskirk et al., 2014). From the authors' perspective, this minimizes the chance of complex alternate dissolution methods to be used for establishing IVIVC/IVIVR as well as the probability of the assessors to recognize their usefulness. On the other hand, it is noteworthy that dissolution specifications used for routine quality control are not commonly driven by clinical pharmacokinetic aspects, but usually evaluated based on quality process-capability related considerations.

With the release of the recent EMA guideline containing instructions on IVIVC reports (EMA, 2015), a more uniform level of submitted IVIVC documentation may be anticipated in the following years. Taking account of the negative attitude expressed by one agency member towards the safe-space concept, demonstrating some kind of "mixed safe space/IVIVC" (Dickinson et al., 2008) might be an appropriate compromise to meet the assessors' challenges. The other two respondents were not negative about the safe-space concept being predefined as part of the IVIVR definition and provided similar answers with regard to IVIVC and IVIVR, respectively, suggesting that they would not generally disapprove of this approach. It is recognized by the authors that there was no in-depth definition of the safe-space concept beforehand and a proven IVIVC or other kind of IVIVRs were not predefined prerequisite within the survey. There appeared to be different opinions about the requirements and applications of this concept from both regulators' and industry's perspective (see also Section 4.2, second paragraph) and scarce information available from the literature so far. In addition, none of the three agency members felt that the IVIVC/IVIVR approach is sufficiently addressed in the existing guidance, indicating that further work might be of value in this field.

5. Concluding remarks

IVIVC/IVIVR plays a role in almost all pharmaceutical companies that were addressed, but success rates, strategies and approaches clearly deviate among the respondents. Notably, there were quantitative and qualitative deficiencies in recording failed attempts. Pursuing an IVIVC/IVIVR should be generally encouraged, considering that the approach seems to be underutilized despite the recognition of its value from both industry and regulators' perspective.

There is not yet much experience with safe-space IVIVRs as well as the use of PBPK modelling in the field of IVIVC according to our survey results. At the same time, the responses from both industry and agencies indicated that there might be a need for a regulatory framework to guide the use of these novel approaches.

Uncertainty on the regulatory acceptance and the lack of appropriate clinical data appear to be critical issues to be focused on for the efficient utilization of IVIVC/IVIVR in drug development. Tackling these problems may require enhanced dialogues between the companies and regulatory agencies as well as within the company itself. While the former aspect is part of ongoing projects within the OrBiTo initiative, the latter one has to be solved within the company-specific framework. The responses indicated that the models were not commonly evaluated based only on studies specifically planned for the purpose of developing an IVIVC/IVIVR. To make the best use of all available information for establishing and interpreting the model, the generation of both *in vitro* and *in vivo* data needs to be optimally coordinated.

It is self-evident that most IVIVC/IVIVR considerations are part of a larger framework, *e.g.* Quality by Design, life-cycle management or drug formulation strategy. *Vice versa*, none of those frameworks would be consistent in the long run if no meaningful link between *in vitro* measurable properties of the drug/formulation and its *in vivo* performance could be established. Since more and more drug candidates are poorly water-soluble, it can be expected that IVIVC development with IR formulations of poorly soluble drugs will attract more attention in the future. For IR products, other types of relationship such as multiple Level C correlation or safe-space IVIVR may be more common outcomes (Table 4). Although achieving a Level A correlation may be the highest motivation with regard to the anticipated regulatory acceptance, it might not be the best criteria for defining success or sorting out models at filing, as suggested by some of the responses. A non-Level A correlation/relationship which is supported by detailed and well documented information substantiating a sound mechanistic understanding might bear the higher potential to reduce the regulatory burden and accelerate formulation development compared to an over-parameterized Level A correlation.

Keeping in mind that the answers to this survey as well as the provided case studies referred to past performances over the last decade, the frequency of use of specific approaches is certainly subject to change. Within the OrBiTo initiative, the collaborative efforts of 27 academic and industry partners focus on the systematic validation of current and improved *in vitro*, *in vivo* and *in silico* biopharmaceutics tools and allows the enormous knowledge gain to be transferred into an industrial framework. Consequently, we expect to see an enhanced use of alternate dissolution methods and PBPK modelling as well as more in-depth evaluation of the physiological factors that affect *in vivo* dissolution and account for inter-/intra-subject variability within IVIVC/IVIVR development.

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Appendix A. Supplementary data

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