[Day 1] 10월 1일(목)	
Bryan Castle | Eli Lilly and Company **[Q2(R2)/Q14] ICH Q2(R2) and Q14: The Enabler for Analytical Procedure Lifecycle, Examples across analytical procedure development, validation and lifecycle management**	
Q 1	During your presentation, you mentioned the importance of continuously monitoring analytical procedure performance in order to determine whether an observed change is attributable to the analytical procedure itself or to a change in the manufacturing process. Could you please share how this type of monitoring is typically performed in practice? In particular, what kinds of metrics, trends, or statistical approaches are commonly used to distinguish method-related variability from variability arising from the manufacturing process, raw materials, or other production-related factors?
A 1	Thank you for the great question. In regards to the presentation, these comments were specific for the muti-variate method (NIR method) used for the determination of ID, Assay, and UDU for a solid oral dosage form. Since this is a model based analytical procedure, diagnostic tests are built directly into the method, specifically Q-residual and Hotelling T2; this is in addition to instrument system suitability (e.g. performance qualification tests) performed prior to analysis. These diagnostics enable real time assessment of the analytical performance by monitoring, 1) spectral variation not present in the calibration (Q-residual) and 2) variation within the model space (Hotelling T^2). A failure would be assessed according to the analytical procedure lifecycle plan (e.g. investigation). In addition, there is also periodic comparison testing between the NIR method and reference method (HPLC), if the acceptance criterion is not met then model maintenance will be triggered according to the analytical procedure lifecycle plan. Further detail on lifecycle management of multivariate procedures, including model maintenance, can be found in ICH Q14 (multivariate section and Annex B) and in the ICH Q2(R2)/Q14 Training Materials, Module 6 (Multivariate Analytical Procedures, Parts A and B).

Q 2	When an analytical procedure is changed, how are the acceptance criteria for a bridging study typically established? For example, how should factors such as the variability and historical performance of the existing method, product specifications, analytical capability, and historical data be taken into account when defining appropriate criteria? In addition, there may be situations where a method change is unavoidable—for example, because a critical reagent, instrument, or raw material has been discontinued—but statistical or technical equivalence between the existing and new methods cannot be fully demonstrated. In such cases, what approaches would you recommend in practice, and what types of scientific justification or supporting data would generally be expected?
A 2	Thank you for the great question. The short answer is that it depends, each procedure change needs to be evaluated via a risk assessment. This risk assessment should take into account what is known about current method, new method, what sample(s) are available for a comparison study, what is the specification, how does this specification define the CQA and connectivity to the QTPP, etc. The output of the risk assessment will guide what should/could be included in the comparison study and the appropriate acceptance criteria. As a reminder, the new procedure must be validated according to the ATP to consistent with ICH Q2(R2) expectations. In the rare case that a bridging study is not possible (e.g. unable to run current method), then following a risk assessment, it is likely that a well characterized sample should be evaluated to confirm that the new method (post method validation) will have acceptable performance and to understand the impact, if any, to the specification/CQA. The key consideration is that from a quality and business perspective you want to have demonstrated confidence that the new method will perform similar to or better than the current method, and still be able to accurately and precisely evaluate the sample. The ICH Q2(R2)/Q14 Training Materials address this in Module 5 (Parts C and D, on risk-based change management and bridging studies), with related content on setting performance criteria in Module 2 Part D and on the ATP in Module 4 Part C.

이명모 (Myungmo Lee)	한국노바티스 (Novartis Korea) [Q8/Q9/Q10] QbD 기반 제품 개발 사례: 위험평가의 재검토에서 관리전략 재수립까지 (A Case Study in QbD-Based Product Development: From an Overturned Risk Assessment to a Rebuilt Control Strategy)	
Q 1	예시를 들어 설명해주셔서 이해가 훨씬 잘되었습니다. 한가지 문의 사항은 200kg으로 스케일업해서 이슈가 된 것을 알게 되면, 시간과 비용이 많이 든 뒤에 입니다. 그런 기회비용을 줄이기 위해, 200kg로 올리기 전에 2kg에서 이슈가 되었던 상호작용의 결과를 확보하는 것이 필요하다고 생각합니다. 200kg 생산 전에 이슈가 되었던 결과를 확보할 수 있는 방법은 아예 없었을지 문의드립니다. Thank you for explaining the example in detail. It helped me understand the issue much more clearly. One question I have is that, if the issue is only identified after scaling up to 200 kg, a significant amount of time and cost may already have been incurred. To reduce such opportunity costs, it seems important to identify the interaction that caused the issue at an earlier stage, such as at the 2 kg or intermediate scale, before proceeding to 200 kg production. In this case, was there any way the issue could have been identified or predicted before reaching the 200 kg scale?	

A 1	좋은 질문입니다. 제 생각에는 이 사례에서 핵심은 "200 kg가 되어야만 알 수 있었는가?"보다 "더 일찍 알 수 있는 기회가 있었는가?"입니다. 실제 데이터를 보면 2 kg에서 92%, 30 kg에서 86%, 200 kg에서 82%로 용출이 점진적으로 감소하고 있습니다. 따라서 200 kg에서 갑자기 발견된 문제라기보다는 30 kg 스케일에서도 이미 경고 신호는 존재했다고 볼 수 있습니다. 만약 개발팀이 30 kg 단계에서 단순히 규격 충족 여부만 보는 것이 아니라, 왜 용출이 감소하는지에 대해 위험평가를 재검토하고 추가 실험을 수행했다면 LOD와 밀링 조건 간의 상호작용을 더 일찍 발견했을 가능성이 있습니다. 따라서 이 사례의 교훈은 반드시 200 kg 생산까지 가야만 알 수 있었다는 것이 아니라, 스케일업 과정에서 나타나는 새로운 데이터에 맞추어 위험평가를 지속적으로 업데이트해야 한다는 점입니다. 이는 ICH Q9(R1)이 강조하는 "risk assessment is not a one-time exercise"라는 메시지와도 연결됩니다. That is a very good question. In my view, the key point in this example is not necessarily “Could the issue only have been identified at 200 kg?”, but rather “Were there opportunities to identify it earlier?” Looking at the actual data, dissolution gradually decreased from 92% at 2 kg, to 86% at 30 kg, and then to 82% at 200 kg. Therefore, this was not an issue that suddenly appeared at the 200 kg scale. There was already a potential warning signal at the 30 kg scale. If the development team had looked beyond simply confirming whether the 30 kg batch met the specification and had instead reassessed the risk associated with the decreasing dissolution trend, additional studies might have identified the interaction between LOD and milling conditions at an earlier stage. Therefore, the key lesson from this example is not that the issue could only have been identified after reaching the 200 kg scale. Rather, risk assessments should be continuously updated as new data emerge during scale-up. This is also consistent with the principle emphasized in ICH Q9(R1) that risk assessment should not be treated as a one-time exercise.

정성훈 (Sunghun Jung) | 삼성바이오로직스 (Samsung Biologics) [Q13] 생물학적 제제 연속제조공정 도입 절차 및 일부 공정 적용 케이스 (Introduction to Continuous Manufacturing for Biological Products and Case Study)	
Q 1	DNA, 펩타이드, 항체, ADC 등 바이오 의약품의 모달리티별 공정 편차를 고려할 때, ICH Q13 관점에서 농도 측정(A280) 외에 IPC 개발 리스크가 적고 연속공정(CM) 적용 난이도가 가장 낮은 모달리티와 실시간 분석법(PAT) 조합은 무엇이라고 생각하십니까? 더불어, CDMO 입장에서 고객사에게 하이브리드 또는 풀 CM을 제안할 때, 초기 견적 상승 부담을 상쇄할 수 있는 수율 향상 및 중장기 절감 측면의 핵심 설득 전략 또는 장점이 있으시다면 어떻게 생각하시는지 궁금합니다. Considering process variability across different biopharmaceutical modalities, such as DNA, peptides, antibodies, and antibody-drug conjugates (ADCs), which modality and process analytical technology (PAT) combination do you think would present the lowest development risk for in-process controls (IPCs) and the lowest barrier to implementation of continuous manufacturing (CM) under ICH Q13, aside from concentration measurement by A280? In addition, from a CDMO perspective, when proposing a hybrid or full continuous manufacturing approach to a client, what would be the key value propositions or business cases to offset concerns about higher upfront costs? In particular, how would you explain the potential benefits in terms of yield improvement and medium- to long-term cost savings?

A 1	ICH Q13에 명시되어 있는 예시를 적용하기 위해선 online LC 가 필요합니다 모달리티의 경우에는 어느정도 히스토리가 축적된 항체의약품일 것 같습니다. 교육때 말씀드린것 처럼 online LC를 도입하면 HMWS 등 impurities를 측정하여 현재 batch manufacturing 에서 수행하는 사전정의된 elution 양만 풀링 하는것이 아닌 각 배치별로 품질허용기준 안에 최대의 양을 pooling 하여 수율을 극대화 할수 있습니다. 또는, DNA 또는 mRNA 의약품 처럼 제품 자체의 안정성이 떨어져 실온 노출시간이 민감한 경우에는 CM 도입을 적극적으로 고려할 수 있을 것 같습니다. 하지만 바이오의약품은 현재로써는 풀 CM은 힘들것 같습니다. To apply the examples described in ICH Q13, an online LC-based analytical system would generally be required. In terms of modality, monoclonal antibodies may currently be the most practical option, as there is already a relatively extensive history and body of manufacturing experience with these products. As mentioned during the training, the introduction of online LC could enable real-time monitoring of product-related impurities such as high-molecular-weight species (HMWS). This would make it possible to move beyond the conventional batch-manufacturing approach of pooling only a predefined elution volume. Instead, each batch could be pooled up to the maximum volume that still meets the predefined quality acceptance criteria, thereby helping to maximize product yield. Continuous manufacturing may also be particularly attractive for products such as DNA- or mRNA-based therapeutics, where product stability is relatively limited and exposure time at room temperature can be critical. In such cases, reducing hold times through continuous processing could offer additional advantages. However, for biopharmaceuticals, full continuous manufacturing remains difficult to implement at present, and a hybrid approach may be more realistic in many cases.

Sheila Inada | AstraZeneca Brazil **[M4Q EWG] ICH M4Q(R2) – a new paradigm for the CMC dossier**	
Q 1	Could you please provide some insight into the expected timeline for SPQS? Once ICH M4Q(R2) is finalized, SPQS may still be at an earlier stage of development. If structured quality information is expected to support future submissions, to what extent will industry be expected to structure the underlying data? For example, would companies be expected to generate and manage raw data in a structured format, or would the requirement mainly apply to the information and data elements submitted in Module 3? Could you also clarify the expected level of granularity and structuring for the data to be included in Module 3?
A 1	SPQS (M16 EWG) is still at an early stage of development. The current work plan is available in the ICH website (https://www.ich.org/page/multidisciplinary-guidelines). M4Q(R2) and SPQS are intended to be complementary. M4Q(R2) provides the framework for the organization of quality information, while SPQS is expected to further enable selected quality information to be represented in a more structured, standardized and reusable format. The precise scope, level of granularity and expectations for structuring Quality information are still to be developed through the M16 EWG. I would therefore see this as an area where continued dialogue and testing with industry and regulators will be particularly important to ensure that the future model delivers the intended benefits while remaining practical and implementable.
Q 2	We understand that future Module 3 submissions may place greater emphasis on structured technical data. Once the relevant guideline is implemented, would companies be expected to provide more detailed or additional technical data than what is currently included in Module 3? Or would the main change be the way existing technical information is structured and submitted, rather than an increase in the overall amount of data required?
A 2	M4Q(R2) is not intended to raise the bar in terms of scientific requirements or the amount of information to be provided. In some cases, R1 did not reflect requirements introduced through ICH Quality Guidelines that were developed after its publication. The main evolution is therefore not necessarily about providing more information, but about how quality information is organized and communicated. Looking ahead, SPQS is expected to build on the M4Q(R2) framework by enabling selected quality information to be represented in a more structured, standardized and reusable format.

[Day 2] 10월 2일(금)	
Jean-Pierre Valentin | UCB, Braine l'Alleud, BELGIUM **[E14/S7B Q & A] Implementing ICH E14/S7B in Practice: An Integrated Approach to QT and Proarrhythmia Risk Assessment**	
Q 1	For a long-acting drug with a prolonged pharmacodynamic effect, for example, lasting approximately one month, how would you recommend designing a cardiovascular safety study? If a consecutive-dose design is used instead of a Latin square or crossover design, and the study is conducted in four animals, would a one-month recovery or washout period be required between each dose level to avoid carryover effects? More generally, what factors should be considered when determining the appropriate interval between dose levels for long-acting compounds?
A 1	The appropriate cardiovascular safety strategy depends first on the therapeutic modality. "Long-acting" describes the duration of exposure or pharmacodynamic activity, but does not indicate whether the compound is a small molecule, monoclonal antibody, large protein, or another modality. Under the August 2026 ICH E14/S7B Q&As (R1), physicochemical properties, mechanistic plausibility for direct hERG interaction, and accrued evidence should be considered together to determine whether a dedicated in vitro hERG and in vivo QTc assessment is warranted. For example, a conventional small molecule would generally require an informative assessment of hERG-mediated delayed repolarisation risk. In contrast, for a qualifying antibody, large protein, or other modality for which direct hERG interaction is considered not likely, a dedicated QTc study may not be necessary solely to evaluate direct hERG-mediated risk. Nevertheless, cardiovascular effects arising from intended target pharmacology, cytokine release, vascular effects, immunogenicity, or other mechanisms should still be considered. If an in vivo cardiovascular assessment is warranted, ICH S7A does not prescribe a fixed washout interval between dose levels. An interval of approximately five elimination half-lives is commonly used as a pharmacokinetic rule of thumb, but it should not be presented as a specific ICH S7A requirement. More importantly, five plasma half-lives may not ensure adequate washout for a compound with active metabolites, tissue accumulation, prolonged receptor occupancy, target-mediated disposition, irreversible or slowly reversible target engagement, or delayed pharmacodynamic effects. Therefore, a one-month washout should not automatically be selected simply because the pharmacodynamic effect lasts approximately one month. The appropriate interval should consider: • the terminal pharmacokinetics of the parent compound and relevant active metabolites; • tissue distribution and accumulation; • duration and reversibility of target engagement and pharmacodynamic activity; • recovery of ECG, heart rate, blood pressure, and other relevant cardiovascular variables;

- the intended clinical dosing regimen and expected accumulation at steady state;
- the temporal relationship among dose, exposure, pharmacodynamic activity, and cardiovascular effects; and
- whether the objective is to assess each dose independently or to characterise cumulative effects under repeated dosing.

If residual exposure or pharmacodynamic activity remains when the next dose is administered, the study should be regarded as a cumulative ascending-dose design, rather than a series of independent dose periods. That design may still be informative, particularly if it reflects the intended clinical regimen, but attribution of an effect to an individual dose level becomes more difficult and interpretation should rely on the complete exposure-response and time-course information.

For a compound with a very long half-life or prolonged pharmacodynamic activity, especially an antibody or another long-acting modality, a traditional four-animal Latin-square or crossover design may be impractical. In this situation, a parallel-group design integrated into a repeat-dose toxicology study may be optimal. This approach avoids carryover between dose levels and can characterise cumulative, chronic, or delayed cardiovascular effects under clinically relevant repeated-exposure conditions. The 2026 ICH training material recommends using ECG assessments from repeat-dose toxicology studies when feasible, provided that the integrated assessment retains comparable scientific and technical rigor.

The integrated cardiovascular assessment should not be limited to QT/QTc. It can include:

- ECG intervals and morphology;
- heart rate;
- cardiac rhythm and arrhythmias; and
- blood pressure, particularly when the target biology, pharmacology, secondary pharmacology, or emerging findings suggest potential haemodynamic, vascular, or autonomic effects.

However, integration into a toxicology study does not justify less robust methods. The cardiovascular component must remain capable of detecting biologically and regulatorily relevant effects. The recording strategy should provide stable physiological baselines, sufficient recording duration, appropriate coverage of anticipated onset, peak exposure or activity, delayed effects and recovery, adequate PK or TK alignment, suitable heart-rate correction, predefined analysis, and control of confounding toxicity.

As highlighted by Valentin JP et al., in Recommendations on the measurement of cardiovascular parameters in non-rodent species for regulatory safety assessment of pharmaceuticals, published in *Current Opinion in Toxicology* in 2026, the recording methodology is a major determinant of data quality, sensitivity, interpretability, and regulatory value. The article identifies ECG, heart rate, and blood pressure as core functional cardiovascular endpoints and recommends telemetry as the preferred standard when cardiovascular monitoring is warranted.

Implanted telemetry is particularly suitable when continuous, long-term ECG and direct arterial blood-pressure measurements are needed. Jacketed telemetry may provide robust ECG and heart-rate data when predefined monitoring windows are sufficient, provided that animal acclimatisation

and data-quality controls are rigorous. By contrast, restraint-based snapshot methods can introduce stress or sedation-related artefacts, increase variability, reduce sensitivity, and compromise physiological and translational interpretation.

Table 2 Comparative Assessment of Cardiovascular Monitoring Methodologies.

Parameter	Restraint-Based	Jacketed-Telemetry	Implanted-Telemetry
ECG, HR, BP	🔴	🟢	🟢
Body Temperature	🔴	🔴	🟢
Baseline values	🔴	🟢	🟢
3Rs impact	🔴	🟢	🟢
Pharmacological sensitivity	🔴	🟢	🟢
Statistical sensitivity	🔴	🟡	🟢
Advanced statistical compatibility	🔴	🟢	🟢
Full TK/TD profile	🔴	🟡	🟢
Clinical translation	🔴	🟡	🟢
Regulatory utility (e.g., TQT waiver)	🔴	🟢	🟢
Study resource (Cost, Analysis, Time)	🟢	🟡	🔴
Operational feasibility	🟢	🟡	🔴

Legend:
- Green – Strong advantage / Best practice / Favorable attribute
- Amber – Context-dependent / Moderate strength
- Red – Major limitation

Clinical translation: clinical relevance of the method. Operational feasibility: ease of study conduct, logistics. 3Rs impact: animal welfare considerations.
This table compares restraint-based, jacketed-telemetry, and implanted-telemetry methodologies across key study parameters and experimental readouts. Jacketed- and implanted-telemetry approaches demonstrate clear advantages in terms of readouts, data quality, sensitivity, translatability, and alignment with 3Rs principles, while restraint-based methods are limited but remain lower in cost and operationally simple. Overall, telemetry-based methods provide superior scientific and ethical value despite higher costs. The assessment is based on the cumulative experience (>150 years) of the authors. ECG, electrocardiogram; BP, blood pressure; HR, heart rate.

Baselines are more stable, more representative, and more comparable across time. Circadian variation can be quantified rather than ignored. Furthermore, group housing mitigates some elevated BP and HR associated with single housing.

Dataset "thickness" and statistical power

RB datasets are intrinsically limited to a few seconds to minutes of recording per time point. Thin datasets have limited statistical power to detect ECG interval changes, and can miss effects (including arrhythmias)

In summary, five half-lives may be a useful initial pharmacokinetic benchmark, but it is neither an explicit ICH S7A requirement nor evidence by itself that carryover has been eliminated. The interval between dose levels should be supported by both PK and PD recovery. When complete washout would make a crossover study excessively prolonged or difficult to interpret, a parallel-group design integrated into a repeat-dose toxicology study may be preferable. Such integration should include ECG, heart rate and, where scientifically relevant, blood pressure, using robust telemetry-based methods capable of generating sensitive, physiologically relevant and exposure-linked data.

임동석 (Dong-Seok Yim) | 가톨릭대학교 의과대학(College of Medicine, The Catholic University of Korea)

[E14/S7B Q & A] ICH E14/S7B의 Q&A 추가에 따른 최근 적용사례 (Cases of ICH E14/S7B Q&A)

Q 1	hERG 결과와 in vivo QT/QTc 결과가 서로 다를 때 어떤 자료에 더 큰 비중을 두어야 하는지 궁금합니다.(예: hERG 결과에서는 유의한 반응이 확인되었으나, in vivo QT/QTc 결과 특이사항이 없을 때) 특히 백신처럼 전신 노출이 매우 낮거나 측정이 어려운 경우에는 hERG IC50의 임상적 의미를 어떻게 해석하고, 비임상 자료를 임상 QT 평가에 어느 정도까지 활용할 수 있을까요? When the hERG assay results and in vivo QT/QTc findings are inconsistent, which type of evidence should generally be given greater weight? For example, how should the results be interpreted if a significant effect is observed in the hERG assay, but no notable QT/QTc findings are seen in an in vivo study? In particular, for products such as vaccines, where systemic exposure is very low or difficult to measure, how should the clinical relevance of the hERG IC50 be interpreted? To what extent can nonclinical data be used to support the clinical QT risk assessment in such cases?
A1	hERG 실험결과와 in vivo 실험에 차이가 난다면 in vivo실험결과가 조금 더 사람의 QT 실험결과와 가까울 것입니다. 그러나 이런 상황에서 임상들어가기 전에 어떤 결론을 내리는 것은 적절치 않으므로 FIH 1상 단계에서 QT를 적극적으로 측정하는 것이 좋습니다. FIH 실험의 경우 건강인에서 therapeutic dose보다 여러 배 높은 용량까지 투여되므로 이 과정에서 QT 측정해서 C-QT 분석을 하면 (+) control 없는 단점을 커버하기 좋습니다. 그리고 백신같은 경우 질문과 같이 전신노출 자체도 극히 낮으므로 E14, S7B의 대상이 되지 않습니다. If the hERG and in vivo study results are inconsistent, the in vivo findings may generally be more representative of the potential QT effects in humans, as they reflect the integrated response of a whole biological system. However, it would not be appropriate to draw a definitive conclusion before entering clinical development based solely on these findings. In such situations, it would be advisable to actively monitor QT during the first-in-human (FIH) Phase 1 study. In FIH studies, healthy volunteers are often exposed to doses several times higher than the anticipated therapeutic dose. Therefore, collecting ECG data across the dose range and conducting a concentration–QT (C-QT) analysis may help address the limitation of not having a positive control. For vaccines, systemic exposure is generally extremely low, as noted in the question. Therefore, ICH E14 and S7B are generally not considered directly applicable to vaccines in the same way as to systemically exposed small-molecule drugs.

한승훈 (Seunghoon Han) | 가톨릭대학교 의과대학(College of Medicine, The Catholic University of Korea) [M15] ICH M15 실제 적용에서의 MIDD 고려사항 (ICH M15 Considerations for MIDD in Practice)	
Q 1	한국 식약처에서 MIDD(PBPK, Pop PK 등) 결과를 인정했던 구체적인 사례가 있을지 문의드립니다. Are there any specific examples in which the Korean Ministry of Food and Drug Safety (MFDS) has accepted MIDD approaches, such as PBPK or population PK modeling?
A1	한국 식약처에서 해당 자료가 폭넓게 인정되고 있습니다. 최근 식약처는 최소한 인체 투여 용량 선정 근거에 비임상 근거 기반 모델링 자료를 거의 routine으로 요청하고 있습니다. 따라서, 제대로 된 신약 파이프라인이라면 한국 식약처에도 최소 1건 이상의 MIDD 관련 자료를 제출한다고 볼 수 있겠습니다. Yes. These types of data are being accepted quite broadly by the MFDS. In recent years, the MFDS has routinely requested modeling results based on nonclinical data, at least as part of the justification for selecting the first-in-human dose. Therefore, for a well-developed new drug program, it would be reasonable to expect that at least one MIDD-related analysis or dataset would be submitted to the MFDS during development.
Q2	모델링 전문 업체 중 추천할 만한 업체가 있을지 문의드립니다. (예: Certain 등 민간 분석업체가 나을지, APACE(서울대 약학 교수님)와 같은 약학 전문 의료진이 있는 기관이 나을지 전문가 소견이 궁금합니다.) Are there any modeling service providers that you would recommend? For example, would it be preferable to work with a private modeling company, such as Certara, or with an academic or medically oriented institution with pharmacometrics expertise, such as APACE? We would appreciate your expert perspective.
A2	COI가 있지만, 객관적인 데이터를 기준으로 말씀 드리겠습니다. 현재 국내 업체 중 모델링 건수 및 규제 대응 경험이 가장 풍부한 업체는 AIMS BioScience입니다. 이 이상 말씀 드리기는 제 position 상 적절하지 않기 때문에 양해를 부탁 드립니다. I would like to note that I have a potential conflict of interest, but I will answer based on objective considerations. Among domestic service providers, AIMS BioScience currently has one of the strongest track records in terms of the number of modeling projects conducted and experience in regulatory interactions. Given my position, however, I believe it would be inappropriate for me to comment further or make a more specific recommendation. Thank you for your understanding.

Shelly Wang | Gilead Sciences **[M15] ICH M15 Guideline: General Principles for Model-Informed Drug Development Practical Application**	
Q 1	When using the MIDD Assessment Table to support early engagement with regulatory authorities, at what stage of development would you recommend initiating the discussion? For example, would it be more appropriate to engage before the IND submission, after completion of Phase 1, or at another key development milestone? What factors should be considered when determining the optimal timing for regulatory interaction?
A1	The MIDD Assessment Table should be introduced once the Question of Interest and proposed MIDD strategy are sufficiently defined, rather than waiting for a specific milestone. The optimal timing is when regulatory feedback can still influence development decisions, study design, or data collection. Regulatory engagement may occur as early as the planning stage (including pre-IND for some applications), but more often, it provides the greatest value before key decisions such as dose selection or pivotal trial design. Factors to consider include the impact of the MIDD approach on decision-making, model risk and uncertainty, availability of supporting data, novelty of the approach, and especially the extent to which the program will rely on the model to support regulatory conclusions.
Vladimir Dragalin | Johnson & Johnson **[E20 EWG] Overview of the ICH E20 Guidance on Adaptive Designs in Clinical Trials**	
Q 1	If an adaptation has been pre-specified in the clinical trial protocol, and the adaptation is subsequently implemented during the ongoing trial based on the results of an interim analysis, what type of communication with the regulatory authority would generally be expected at the time of implementation? If no additional regulatory communication or submission is required at that stage, would it be sufficient to appropriately document the adaptation, including the rationale and implementation process, and report the relevant information in the final clinical study report (CSR)? Are there any particular circumstances in which a pre-specified adaptation would still require prior consultation with, or notification to, the regulatory authority?

A1	At the time of implementation of a pre-specified adaptation, there is no need to interact with regulatory authority. The Chair of the IDMC communicates the recommendation for adaptation to the Sponsor Steering Committee (for complex adaptive designs, e.g. treatment selection or population selection) or to the representative of operational systems, e.g. IWRS, according to the process established in the IDMC Charter. However, the recommendation should appropriately be documented and made available to the Sponsor at the end of the study. In case of the IDMC recommendation to stop the trial, the Sponsor may decide to consult with the regularity authority before taking the final decision.