2020년 ICH 가이드라인 교육
강연별 질의응답 취합본

강연	연사
M1 - MedDRA 활용: 코딩 및 데이터 분석	도윤희
Q1	**Coding 시 Primary SOC 가 아닌 Secondary SOC로 배정 하기를 요청 받은 경우, Primary SOC를 우선적으로 선택해야 한다는 근거 자료를 어떻게 제시할 수 있을까요?**
	'MedDRA 용어 선택: 고려 사항' 문서의 일반 용어 선택 원칙 중 섹션 2.3 MedDRA 변경 금지에 관한 내용이 있으므로 이를 발췌하여 사용하실 수 있습니다. **2.3 Do Not Alter MedDRA** MedDRA is a **standardised** terminology with a pre-defined term hierarchy that should not be altered. Users must not make *ad hoc* structural alterations to MedDRA, including changing the primary SOC allocation; doing so would compromise the integrity of this standard. If terms are found to be incorrectly placed in the MedDRA hierarchy, a change request should be submitted to the MSSO. 또한, 'MedDRA 모범 사례(MedDRA Best Practices)'라고 하는 참고 문서가 있는데, 이 문서의 섹션 2에서도 동일한 내용을 좀 더 자세하게 설명하고 있습니다. 코딩을 할 때, SOC 정보는 선택하는 것이 아니고, LLT를 선택하면 그에 따르는 계층 정보를 그대로 따라야 한다는 내용입니다. **2. PRIMARY SYSTEM ORGAN CLASS (SOC) ALLOCATION IN MedDRA** **2.1 PURPOSE** This section explains the concept of the primary System Organ Class (SOC) allocation in MedDRA and why the primary SOC should not be individually selected by MedDRA users. To do so undermines one of the main goals in using MedDRA as a regulatory standard. 위 두 문서는 모두 MedDRA 홈페이지 How to use > Support Documentation 페이지(https://www.meddra.org/how-to-use/support-documentation) 에서 다운로드 받으실 수 있습니다.
Q2	**연습문제 답은 알려주시면 감사하겠습니다**
	첨부파일(pdf) 참고 바랍니다.
Q3	**WHO ART 랑 MedDRA은 무슨 차이가 있나요?**
	WHO-ART의 경우, WHO-UMC(Uppsala Monitoring Centre)에서 이상 사례 보고를 위해 개발, 배포 하던 용어집 입니다. 이에 비해 MedDRA는 아무래도 의약품 전 규제 과정에서 활용할 수 있도록 고안되었기 때문에 다루는 범위가 넓고 구체적이어서 용어 수도 많습니다. 두 용어집은 구조적으로 유사한 부분이 있지만, WHO-ART의 경우 4계층, MedDRA는 5계층 구조로 되어 있는 것이 큰 차이점 입니다. 2015년 이후로는 UMC에서도 ICH표준인 MedDRA를 사용하기 위하여 더 이상 업데이트하고 있지 않으며, 현재 계속해서 MSSO와 함께 브릿지 파일을 업데이트하고 있습니다.
Q4	**코딩 연습 4 에서 질의 사항이 있어 메일 드립니다. (p.68)** **<Patient accidentally 1) took drug Y instead of drug X and became 2) short of breath.> 예시와 관련하여 1)번과 2)번 각각에 대해 각각 하기와 같이 coding 을 해 주셨는데 이 경우에는 최종적으로 둘 중 어떤 것으로 coding 이 더 정확한 코딩인지 문의 드립니다. 아니면 event 를 2 개로 수집하여 1), 2) 각각으로 coding 해야 하는 것인지요?**
	네, 코딩 연습 4 에서는 두 개를 모두 선택하는 것이 맞는 코딩 입니다. 보고된 이상 사례의 내용을 코딩할 때, 둘 이상의 MedDRA 용어를 선택하여 더 많은 정보를 제공할 수 있다면, 분할하여 코딩할 수 있습니다. 해당 내용은 'MedDRA 용어 선택: 고려 사항' 문서의 섹션 3.5.4 에서 확인하실 수 있습니다.
M4 - 국제공통기술문서	이정욱
Q1	**품목허가 말고도, 임상승인시에도 CTD 로 작성되어야 하나요?**
	신청제품의 특성에 따라 작성하시면 됩니다. 기존 제품의 제형변경과 같은 경우는 복잡하지 않겠지만, 신약의 제제개발이나 새로운 제형과 같은 경우 평가해야 할 항목이 많아지므로 내용이 많을 수 밖에 없습니다. 3.2.P 항에는 상세히 쓰시고, 2.3에는 요약하여 작성하시면 되겠습니다.
Q2	**QbD 를 적용하여 개발한 제품의 경우, 위험평가표나 DoE 자료들을 3.2.P 항에 얼마나 자세히 넣나요? 너무 길게 쓰면 싫어하나요?**
	식약처 고시 "의약품 임상시험 계획 승인에 관한 규정"에 의거, 임상시험계획승인신청서에 첨부하여야할 임상시험용의약품 품질평가자료는 동 고시 별표 3,4 에 의거 CTD 유사양식으로 작성하여야 합니다만, 별표의 섹션 타이틀을 보시면 CTD Module 2.3 을 약간 변형하였음을 알 수 있습니다. 미국에 IND 제출 시는 CTD 양식으로 작성하여 eCTD 로 제출하여야 합니다.
M9 - ICH M9 생물약제학적 분류체계 근거 생동면제	James Mann / Xavier Pepin
Q1	**혹시 BCS waiver 를 통해 허가된 해외사례가 있나요?**
	James Mann ➔ I am not aware of anyone using ICH M9 yet as many countries are still in the process of updating there local guidance/regulations to align with ICH M9, I suspect it will be used many times in the coming years though. Many companies have exploited BCS biowaivers in the territories where this has been part of the guidance for many years (e.g. USA/EU etc), however sometimes they may have been forced to generate different experimental packages to fulfil the unique elements of the different territorial requirements.
	Xavier Pepin ➔ To build on James' comment, there are also a large body of evidence in the literature for supporting BCS classification of essential drugs. Here are below a few examples and commentaries 1. C. L. Cheng *et al.*, Biowaiver extension potential to BCS Class III high solubility-low permeability drugs: bridging evidence for metformin immediate-release tablet. *Eur J Pharm Sci* **22**, 297-304 (2004). 2. L. Kalantzi *et al.*, Biowaiver monographs for immediate release solid oral dosage forms: acetaminophen (paracetamol). *J Pharm Sci* **95**, 4-14 (2006). 3. C. Becker *et al.*, Biowaiver monographs for immediate release solid oral dosage forms: isoniazid. *J Pharm Sci* **96**, 522-531 (2007). 4. C. Becker *et al.*, Biowaiver monographs for immediate release solid oral dosage forms: ethambutol dihydrochloride. *J Pharm Sci* **97**, 1350-1360 (2008).

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6. S. Grube *et al.*, Biowaiver monographs for immediate release solid oral dosage forms: Quinidine sulfate. *Journal of Pharmaceutical Sciences* **98**, 2238-2251 (2009).
7. A. Okumu, M. DiMaso, R. Lobenberg, Computer simulations using GastroPlus to justify a biowaiver for etoricoxib solid oral drug products. *Eur J Pharm Biopharm* **72**, 91-98 (2009).
8. Y. Tsume, G. L. Amidon, The Biowaiver Extension for BCS Class III Drugs: The Effect of Dissolution Rate on the Bioequivalence of BCS Class III Immediate-Release Drugs Predicted by Computer Simulation. *Molecular Pharmaceutics* **7**, 1235-1243 (2010).
9. C. Alvarez *et al.*, Investigation on the possibility of biowaivers for ibuprofen. *J Pharm Sci* **100**, 2343-2349 (2011).
10. J. R. Crison *et al.*, Biowaiver Approach for Biopharmaceutics Classification System Class 3 Compound Metformin Hydrochloride Using In Silico Modeling. *Journal of Pharmaceutical Sciences* **101**, 1773-1782 (2012).
11. J. B. Dressman *et al.*, Biowaiver Monograph for Immediate-Release Solid Oral Dosage Forms: Acetylsalicylic Acid. *Journal of Pharmaceutical Sciences* **101**, 2653-2667 (2012).
12. R. Cristofoletti *et al.*, Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Efavirenz. *Journal of Pharmaceutical Sciences* **102**, 318-329 (2013).
13. S. Colon-Useche *et al.*, Investigating the Discriminatory Power of BCS-Biowaiver in Vitro Methodology to Detect Bioavailability Differences between Immediate Release Products Containing a Class I Drug. *Mol Pharm* **12**, 3167-3174 (2015).
14. N. A. Kasim *et al.*, Molecular Properties of WHO Essential Drugs and Provisional Biopharmaceutical Classification. *Molecular Pharmaceutics* **1**, 85-96 (2004).

강연	연사
E2B(R3) - E2B(R3) 품질향상을 위한 개별사례 안전성 보고	Jean Christophe Delumeau

Q1	CIOMS 종이 보고서 형식은 어떻게 이용하게 되나요?
	I would like to respond to the question "How can we utilize the CIOMS report format". As emphasised in my presentation, the CIOMS-1 Form is a 30-year old and outdated way to collect ICSR information. According to ICH, only E2B(R3) is considered ICH-compliant. For this reason, the WHO-UMC will soon launch an online tool for reporting ICSRs from a keyboard in a E2B(R3)-compliant manner. However, this on-line tool will be available only in countries where the National Regulatory Authority is using the VigiFlow system supplied by the UMC. This being said, to report a case to the Market Authorisation Holder (MAH) of Korean Authority, you may be using a CIOMS form. Then, the Health Authority or the MAH will be entering the case into an E2B(R3) database. Then, in order to get the detailed information that the CIOMS-1 form is not designed to collect, they will re-contact the Reporter which with actually constitute a repeated collection of information.

E2C(R2) - PBRER과 DSUR 준비 방법 - ICH E2C와 ICH E2F	Dawn Ren

Q1	DSUR 과 PSUR 의 차이는 무엇인가요?
	먼저, DSUR 과 PSUR 의 요건 자체가 다릅니다. DSUR 의 경우 사실 개발과 관련된 부분입니다. 국제적으로 이루어지는 임상과 관련 되어 있는 것이죠. 그런 경우라면 DSUR 을 제출해야 합니다. PSUR 의 경우는 이미 시판중인 제품에 관한 것 입니다. NDA 가 없다면, PSUR 을 제출 할 이유가 없습니다. 그러니까 시판 허가를 보유하고있는 허가권자가 아니라면 PSUR 을 제출 할 이유가 없습니다. 그리고 DSUR 의 경우에는 포스트 마케팅 데이터는 당연히 중요하지 않습니다. 이것은 임상시험 관련 데이터가 중점이 될 것이고요. 그리고 이 내용을 보게 되면, DSUR 의 내용이 PSUR 에 다 들어가게 되어있습니다. 그래서 내용으로 보자면, 큰 차이가 있다고 말하기는 어렵습니다. 16 번 섹션을 보면, 위해성과 관련된 부분이 많이 들어가 있습니다. DSUR 의 경우에는 이 관련 자세한 내용이 그렇게 많이 들어갈 필요가 없습니다. 카테고리 정도면 됩니다. 내용에 대해서는 아주 자세히 들어갈 필요가 없습니다. 임상 같은 경우에는, 사실 같다고 볼 수 있습니다. DSUR 을 작성했고, 제품이 이미 시판 중이라면 PSUR 관련해서는 DSUR 내용에 더불어 포스트 마케팅 관련 된 내용이 들어가야 합니다. 내용적으로는 이 차이가 있습니다.
Q2	For generic products, several companies each collect safety information respectively. In this case, who write a PBRER? is it each company write a PBRER with the information that they have? Or only the company of the original product write a PBRER?
	No matter if it is an originator or a generic, as long as the company has the product on the market, the company has to submit a PBRER for the data they received.
Q3	It seems that the literature search rely on the company's capabilities. Are there search terms commonly recommended to use for DSUR or PERER? Or each company should decide search terms considering their benefit/risk of product?
	Review of the literature requires some medical knowledge. The search strategy for a medical topic varies, depending on different topics; MedDRA SMQ is most recommended.
Q4	장기적으로 사용하는 약물의 경우 환자노출정보 계산이 어려울 수 있는데 혹시 도움이 될 만한 경험이 있으면 공유 부탁드립니다.
	It is true that for very old products, the cumulative exposure data are often unavailable. The company may focus more on periodic exposure data. A recommendation is: the company explains in PBRER that cumulative exposure data is not available, patient exposure data is estimated since when…. Then the later report can be compared with the former report.

강연	연사
S6과 M3 비교	Jian Wang

Q1	What kinds of bridging studies needed in case of using the different product formulation between non clinical and clinical study?
	For most of the cases, a bridging study may not be required, if the drug substance is the same and formulation is relatively simple. You can address the differences by doing comparative human PK studies. However, if formulation has changed for the modified release tablet, a bridging safety study would be required to demonstrate comparable PK profile.
Q2	FDA 가이드라인 중 'Endotoxin testing for single-use intraocular ophthalmic Devices' 내용이 있던데, 이 경우는 주로 TASS 예방을 위해 확정된 지침으로 알고 있으며, 보통 영구 임플란트나 안구내 수술시 사용되는 일회용 장치나 안구내 조직 보호를 위한 안구내 점액성 물질등에 대한 test 로 알고 있습니다. Intravitreal injection 하는 항체의약품의 경우에도 동물에서 Endotoxin test 를 진행 하는게 맞는 걸까요?
	I am not the expert to answer the 2nd question, as I am not doing device.

강연	연사
ICH Q12: 의약품 전주기 관리	Jean-Louis Robert

Q1	PACMP 가 mandatory 가 아니라 chemical 제품의 경우, 아직 많이 하지는 않은 것 같은데요. PACMP 제출해서 변경할 경우, 프로토콜 승인은 별도로 필요한지요? 아니면 PACMP 제출후 보고서만 내면 되는지요?
	제가 즉각적으로 답할 수는 없는 부분이니, 운영진 혹은 이메일을 통해 질문주시기 바랍니다. 이 변경사항과 관련하여, 변경을 적용하고 그 계획서를 제출해서 승인을 받으면 되는 건가요? 라는 질문인데, 계획서는 의무사항은 아닙니다. 이것은 하나의 Tool 입니다. 즉, 계획서를 사전에 승인 받는 것이 필요하냐는 질문인데, 의무사항은 아닙니다. 그래서 무언가 변경을 한다, 변경 계획서를 제출하는데 이 때 대대적인 변경에 해당하는 경우에는 사전에 계획서에 대한 승인을 받는 것이 필요합니다. 사소한 변경의 경우에는 그렇지 않습니다. 대대적인 변경의 경우에는 당연히 새로운 계획서를 제출하 셔야 하고 승인이 필요합니다. 규제 담당자로서, 이 계획서에 대한 재승인이 필요하다고 판단이 됩니다.

ICH Q12 이행 사례	Frank Montgomery

Q1	Established conditions may vary between regulatory bodies. Do you have experience or suggestions on how to approach the differences between the regulatory bodies?
	좋은 질문입니다. 아주 많이 하시는 질문들 중 하나입니다. 현재 상황이 그러합니다. 허가 후 변경과 관련해서 관리항목을 어떻게 운영할 것이냐 라는 관점에서 보면, 많은 국가에서 서로 다른 방식으로 이것을 채택하라고 하거나, 또는 우리의 관리 전략을 변경하도록 한다든가 여러 차이가 있습니다. 지금도 그렇지만, 이와 관련 된 것이 지속될 것으로 생각됩니다. 저희가 직접적 경험은 없습니다. FDA 관리항목 관련 파일럿 스터디에 참여를 한 적이 있습니다. 다만, 우리가 무언가를 관리항목으로 제시할 때는 현실적이어야 한다는 것, 또한 이와 관련하여 매우 강건한 Justification 을 제공해야하다는 것입니다. 그렇게 하면, 서로 다른 지역의 규제기관 당국간의 최소한 조금 더 유사한 결론을 갖게 될 것입니다. ICH 가 이런 가이드라인 이행에 대해 서로 다른 지역에서 어떻게 이행되고 있는지 지속적으로 모니터링 하고 있습니다. 시간이 되면 좀 더 개선될 것입니다.
Q2	Not many countries have PACMP in their regulations yet. Does AZ have experience in getting approval for PACMP in such countries? Also for nonPACmP adopting countries do you have any suggestions on resolving the different timelines for getting approval for a change in different countries?
	현재 PACMP 가 규제에 반영되어 있는 국가는 유럽과 미국입니다. 스위스가 도입을 했지만, 아직 이행을 하지는 않았습니다. 그래서, EU 와 미국에만 이행이 되어 있습니다. 저희가 양국에 PACMP 경험이 있고, 유럽에서 최근 Site Transfer Case 가 있었습니다. 그리고 생물학적 제제의 시험에 대한 내용을 신청한 바 있습니다. 이러한 변경을 통해 Brexit 의 원래 일정보다 앞당겨 진행을 했습니다. 만약 Brexit 이 진행되었다면, 공급 계획에 차질이 생겼을 것이고 굉장히 심각한 상황이 벌어졌을 것입니다. 이 경우에 허가 후 변경관리 계획서를 도입함으로써, 잘 진행되었습니다. 만약 PACMP 가 없었다면, 굉장히 어려운 상황이 되었을 것입니다. 승인기간 단축 관련하여 이를 가능하게 하는 유일한 방법은 사실 규제당국과 협의하는 것 입니다. 해당 변경이 특정 분류 카테고리에 해당이 되는가, 이는 지식과 위해성에 대한 평가를 기준으로 이루어져 '이 것이 위해도가 낮은 카테고리이다' 라고 합의하고, 더 신속하게 도입할 수 있도록 하는 것 입니다. 사실 이렇게 하기 위해서는 굉장히 강력한 타당성 자료가 필요할 것이고, 지역별로 다를 것 입니다. 지역별, 국가별로, 규제당국이 얼마나 개방 된 자세를 취하고 있느냐 에 따라 달라지겠죠. ICH 가 도입 된 많은 지역과 국가에서, 시판 후 승인에 대한 Framework 를 도입하고 있고, 또 비효율적인 시판 후 Process 가 가져다 주는 그런 어려움에 대해 잘 인지하고 있습니다. 많은 규제당국에서 실제로 이로 인해 부과되는 많은 업무로 인해 어려움을 겪고 있습니다. 따라서, 환자에게도 그렇고, 규제 당국의 관점에서도 그렇고, 불필요한 과정이라 판단되는 경우이기 때문에 가이던스와 Regulation 을 통해 시판 후의 변경을 이행하는 것에 대해 Global 차원에서 개선하기 위해 노력하고 있습니다. 이런 방향이 지속되길 바랍니다.
Q3	QbD 전주기 관리를 하면, 제조사는 어떤 이점이 있나?
	QbD 는 굉장히 탄탄한 과학입니다. 과학적으로 탄탄하다는 것은 비즈니스에도 좋다는 이야기가 될 것 같습니다. 좋은 비즈니스라는 것은 '제조'에 있어서 만약 어떤 문제가 발생한다면, 더욱 더 빠르게 그 원인을 파악하고 문제를 긍정적 방향으로 해결할 수 있고, 또 우리가 규제당국과 관련 된 관련 제 규정준수를 좀 더 강화할 수 있다는 것입니다. 굉장히 중요한 것이라고 생각합니다. 제가 오늘 발표하며, 미국 내 제품관련 관리항목들을 공유했는데, 이 관리 항목은 우리에게 많은 도움이 되었습니다. 우리가 변경을 할 때, 규제당국과 특별히 별도로 Communication 하지 않고, 저희의 Quality Management System 내에서 빠르게 진행할 수 있는 여지를 주었습니다. 이는 QbD 접근법을 채택했기 때문입니다. 이 사례들을 보면, 굉장히 많은 불순물 Tracking 을 했고, 공정에 대한 이해를 높이는 작업을 많이 했습니다. 이것이 제조공정 개발에 도움이 되었죠. 또한 Design Space 를 관리전략의 일환으로 제안했었고, QbD 같은 경우에는 사실 Design Space 라고 보기 보다는 훨씬 더 탄탄한 과학적 접근법이면서, 좀 더 강력한 관리방법이라고 생각합니다. 저는 강력하게 추천합니다.
Q4	QbD 전주기 관리를 하면, 규제 유연성 측면에서 제조사에 어떤 것이 제공되나?
	Site 변경을 하는데 있어서, 우리가 가지고 있던 안전성 데이터를 사전에 제출하지 않았다면, 이는 불가능했을 것 입니다. 저희 QbD, 원료 의약품에 대한 지식, 그리고 '안전성에 영향이 없다'라는 데이터를 가지고 FDA 와 논의하여 Site 변경을 할 수 있었고, 안전성 데이터는 사전에 제출 할 필요가 없었습니다. 연례 보고서에서 안전성 데이터를 제출했고, 이는 변경 후에 제출 된 것입니다. 임상적으로 굉장히 중요한 의약품이고, 빠르게

	성장하고 있는 의약품이며, 이 공급망을 신속하게 확장하는 것이 중요했습니다. 환자들에게 충분하게 공급하는 것이 중요했기 때문에, 이렇게 진행했고 이 경우에서 봤듯이 의약품에 대한 지식과 공정에 대한 이해가 높을 수록 유연한 규제당국의 대응을 기대할 수 있었습니다. 이 사례를 통해 전달된 것 처럼, 출발 물질과 관련 된 규격을 단순화하는 것, 사실 이것도 까다로운 작업이고 변경하기에 간단한 부분은 아니었지만, 이런 많은 항목들이 있었습니다.
ICH Q8, 9, 10 접근방법에 대한 전략적 해석	김태규
Q1	**CQA 를 선정할 때 RA 를 수행한다고 하셨는데, 기존지식 및 데이터가 충분히 확보되었을 때에도 반드시 RA 를 수행해야 할까요?**
	네, CQA 선정 시 Risk Assessment 를 당연히 따라야 합니다. 기존 지식 및 데이터가 충분히 확보되어 있다는 것 역시, 그 지식의 정도가 '이것이다' 라고 표현하는 것 자체도 Risk Assessment 라고 생각합니다. 제가 볼때는 반드시 RA 를 수행하고, 그에 대한 정당성, 당위성, Evidence 를 갖추는 것이 중요하다고 생각됩니다.
Q2	**RA 를 위한 다양한 Tool 이 제시되어 있는데, 각 Tool 의 장단점은 어떻게 되며, 국내 제약업계의 상황에서 가장 적절한 Tool 은 무엇이라고 생각하시는지요?**
	ICH Q9 에서, RA 를 할 때 사용할 수 있는 다양한 방법이 제시되고 있습니다. 그래서 어떤 방법이 가장 적합하다고 설명 드리기는 조금 곤란합니다. 저 같은 경우, 또한 국내 제약업계에서 가장 대표적으로 쓰이는 것들이 FMEA 나 혹은 FMECA 방법입니다. 그렇지만 FMEA 나 혹은 FMECA 방법을 쓰기 위해서, 프로세스 매핑이나 프로세스 체크시트, Cause&Effect Diagram 등의 적절한 도움을 받아서 FMEA 나 혹은 FMECA 방법을 사용하고 있다고 설명드릴 수 있습니다.
Q3	**전 분야의 전문가(개발, 연구, 생산, 마케팅 등)들이 참여해야 한다고 하셨는데, 가령 공정에 대한 RA 를 진행한다고 하였을 때, 이에 대한 이해도가 낮은 분야의 인원 등으로 인해 RA 가 올바르지 않게 수행될 위험은 없는지요?**
	아주 좋은 질문입니다. 각각의 전문가들이 다 참여하는 것이 아주 중요합니다. 제가 개인적으로 생각하기에, 이해도가 낮은 부분에서도 언젠가는 그 분의 진가가 나올 수가 있기 때문에 되도록이면 각 분야의 전문가들을 대동시키고, 그 분들이 Risk Management 에서 가장 중요한 Risk Communication 과 이 안에서 중요한 리더십을 발휘하여 잘 이끌어간다면, 비전문가가 참여한다고 하여 Risk Assessment 가 위험하게 되지 않을 것 같습니다. 그래서 저는 개인적으로, 많은 사람들이 Risk Assessment 에 참여해주는 것을 권고드리고 있습니다.
Q4	**RA 를 적절하게 수행하지 못하였을때 어떤 문제상황이 발생할 수 있으며, 이에 대한 해결방안은 어떻게 될까요?**
	RA 를 수행하지 않으면 일단, QbD 허가 불가입니다. 또한 설계 공간 및 CCP 등의 선정 등을 위한 파라메터 선정에서 적절성이 떨어지므로 이후 연구는 규제기관으로 부터 설득력 있는 답변이 불가할 것으로 사료됩니다. 이에 대한 해결은 RA 를 수행해야 합니다. 이것은 필요충분 조건 입니다.
Q5	**제품 특히 의약품 개발과정에서 다양한 파라미터의 연관성을 파악하는데 DoE 와 QbD 등의 툴이 통계적인 데이터를 뒷받침에 도움이 되겠지만 과연 이들의 통계적인 영향력을 과학적인, 통계툴로서의 정확성을 뒷받침하기위해서 진행해야하는 실험의 반복횟수가 많이 증가하게될것이라고 생각이 드는데요 혹시 오랫동안 관련 연구 업무를 진행하신 경험을 바탕으로 보실때 얼마나 반복해서 신뢰도를 입증혹은 완료할수있을까요??**
	QbD 내에서 DoE 의 목적은 "최소의 실험으로 최대의 데이터를 확보 하는 것"이라고 설명드리고 싶습니다. 통계적 툴을 이용하여 유의성 있는 데이터를 얻는 것은 RA 를 통해 얼마나 효율적인 Parameter 를 선정했고, 그 Parameter 를 토대로 DoE 를 얼마나 잘 실험디자인을 했는냐가 관건일 것 입니다. 통상 의약품 QbD 에서의 DoE 는 반복실험 등은 하지 않습니다. 반복실험을 하지 않는 이유는 2 번, 3 번 반복한 결과가 더 유의한 데이터로서의 시뮬레이션이 된다는 보장은 없습니다. 적절한 실험디자인(DoE)으로 실험을 수행한 후 효과적인 시뮬레이션 기법 (몬테카를로 시뮬레이션 등)을 활용하여 해보지 않은 100 만번, 10 만번의 Run 을 구현하여 그 결과를 예측하는 방법을 추천합니다.
Q6	**신약을 신규 제조소에서 제조한다고 했을 때, P/S/D 스코어를 메기기 위한 충분한 통계자료가 없을 수 있습니다. RA 는 평가자의 의견이 들어가기 때문에 이러한 통계 자료 등의 객관적인 근거자료를 가지고 평가하지 않을 경우 주관적인 평가로 치부될 수 있을 것 같은데 이에 대한 해결방법에는 무엇이 있을까요?**
	적절한 P/S/D 는 반드시 제조소에서 행해지는 것이 아닙니다. 연구개발 단계에서 수행하는 것이므로 연구개발 단계에 맞는 RA 가 추진되어야 하며, 그것에대한 객관적 근거 역시 연구개발 단계에서의 솔직(?)한 위험평가가 실행된다면 위험을 줄일 수 있는 활동이 결국 GMP 로 기술이전 할 때 조건사항, 개선사항 등으로 전달될 좋은 결과일 것 입니다. 주간적인 RA 는 있을 수 없는 것이며, RA 수행에 대한 근거는 과학적, 경험적, 이론적 합리성에서 나와야 합니다. 과학적, 경험적, 이론적 합리성이 결여되었따면 이것은 위험이 높은 것이므로 이것에 대한 위험을 줄이는 것이 오히려 좋은 해결방안일 것 입니다.
Q7	**규제기관에서 인정하시는 전문가기준이 있으신지요? 제조사별로 전문가를 구축하여 연구 및 제품개발을 진행하고있지만 관리 규제기관에서 보장하는 전문가의 기준이 있는지 궁금합니다.**
	전문가 기준은 없습니다. 제 개인적인 생각에는 과장(책임급)급 이상의 업력 6 년차 이상의 경력자로 구성한다면 큰 문제는 없을 것 같으며, 규제기관에서 볼때도 해당제품의 전문가는 해당회사의 해당 공정을 다루는 사람이므로 그 누구도 전문가에 대한 자질(?) 의심은 없을 것 같습니다. 극히 제 주관적 입니다.
Q8	**국내는 아무래도 제네릭시장이 우세합니다. 제네릭의약품을 신규 제조소에서 생산한다고 했을 때 QbD 를 통한 CQA, CPP 설정이 효과적이라고 볼 수 있을까요?**
	네, 국내 같은 경우가 그러합니다. 국내는 제네릭 의약품이 많이 있다보니, 대부분 Origin 약품을 통해 이미 CQA 가 선정되어 있죠. CQA 는 선정되어있을 수 있지만, 그 제품 특성에서 CPP 는 설정해야될 것 같습니다. 그 제조사의 장비도 다를 것이며, 생산 환경도 다를 것이며, 프로세스도 조금씩은 다를 것 입니다. 모든 환경에서 제품이 동일하게 제품화되지는 않습니다. CPP 는 프로세스 파라메터의 중요도를 이야기합니다. 때문에, 제네릭 의약품의 경우 그 회사 자체적으로 CQA 는 미리 설정될 수 있습니다. 하지만 CPP 는, 제네릭 의약품의 예를 들어, Tablet 제품이라면 경도, 압력 등으로 인해 품질의 완성도가 높을수도, 낮을수도 있습니다. 이는 장비와도 연관성이 있고, 어떤 특정 의약품과의 혼합과도 연관성이 있을 수 있고, 포장과 연관성이 있을 수도 있습니다. 이러한 것들을 우리가 밝혀내서, 결국 우리 제품의 CPP 는 '압력'이다, '온도'이다 등으로 규정해야 한다고 생각합니다.

Q9	저도 비슷한 질문 드리고 싶습니다. 국내 제품개발 연구비와 규모로 볼때 과연 QbD 기반의 제품개발이 우선시되어야하는것인지 의문입니다. 국내 개발상황에 적합한 융합형 관리방안이 마련될 기회가 있는지 궁금합니다.
	너무 어려운 질문이라 융합형 관리방안 등 질의에는 답변드리지 못해 죄송합니다. 다만, 오해가 있으신 것 같아 명확히 해드리고 싶습니다. QbD 가 개발비용이 많이 든다(?)에는 동의하지 못할 것 같습니다. 지금 연구개발 하시는 것에서 조금 더 체계화된, 구체화된 연구개발을 하는 것이 QbD 라 생각됩니다. TPP 부터 타깃하는 제품을 규정하고, 타깃하는 제품의 제형을 결정하고, 제형을 결정하면 안정성 연한의 목표가 생기고, 안전성과 유효성을 유지하고 문제가 없도록 공정 특성을 규명하고, 공정특성에 맞는 CCP 등을 인지하고 그것을 관리하는 전략을 꾸리는 것이 QbD 일 것입니다. 제 개인적인 생각엔 지금 말씀드리는 것에 대한 문서화 비용, 시간을 필요할 것이고, 공정특성을 밝히는 작업은 보다 더 진보적인 실험계획법에 따라 수행하고 평가하는 것이 전부입니다. 즉, 체계화하는 작업비용 정도의 추가비가 전부일 것입니다. 지금껏 정확한 개념이나 방식이 없이 연구개발했던 페러다임에서 실험을 하더라고 무엇을 얻을 것이며, 같은 실험을 하더라도 2~5 가지의 목적을 달성하는 실험계획이 잡힌다면 비용은 기존대비 큰 차이는 없을 것으로 생각됩니다. 생각을 바꾸고, 변화하는 것에 조금의 투자가 된다면 보다 더 많은 비용절감, 생산성 향상, 제품공정에 대한 지식확보가 가능할 것으로 보입니다.

강연	연사
산업계 측면에서의 ICH Q-trio 해석 및 실행	김현철

Q1	PURSIT 의 경우, 설비 특성상 post - sterilization integrity testing 을 할 수 없는 경우가 있는데요(아이솔레이트 사용)이럴 경우 어떻게 해결을 해야 할까요?
	많은 분들께서 실제 고민하고 계신걸로 알고 있습니다. 그리고 실제 실행하다보면 이 것은 굉장히 어려운 기술입니다. 많은 공간도 필요하고요. 저의 짧은 경험에 의하면, 최근에는 이 PURSIT 을 구현할 수 있는 일회용 Disposable Package 가 있는 것으로 알고있습니다. 설비 특성상 영구적으로 PURSIT 을 구현하기 어렵다면, 이런 Disposable Package 를 고려해보시는 것이 어떨까 생각합니다.
Q2	말씀하셨다시피 PQS 는 명확한 지침이 제시되지 않아 이해하는데 있어 어려움이 있습니다. 제약업체 자체적인 방법으로 위해평가를 실시하여 관리해야 하는 상황에서, 그렇다면 자체적으로 실시한 RA 와 이에 따른 관리조치를 제약업체가 규제당국에게 제시하였을 때 규제당국은 어떠한 기준으로 이에 대한 평가를 하게 되는지요?
	좋은 질문을 해 주셨습니다. 저는 식약처에서 근무하는 사람이 아니다 보니, 규제당국에서 어떻게 생각하시는 지 100% 다 말씀드릴 수 없지만, 실사를 받을 때나 혹은 규제당국에 계신 분들과 의견을 나눌 때 제가 이해한 바에 의하면 대략 이런 듯 합니다. 여러분들이 아시는 바와 같이, 현재 ICH Q9 이 실제 발행되지 않았지만, 이의 Revision 이 진행중입니다. ICH Q9 의 QRM 에서 가장 큰 단점이 '주관성'인데, 즉 'QRM'을 하라고 하니 업계가 주관적으로 Risk 가 너무 큰 것에 대해 '괜찮다'라고 평가하는 것입니다. 이것이 QRM 의 가장 큰 단점인데, 그래서 그 Q9 에서 이 '주관성'을 어떻게 극복할 것인가에 대해 여러 전문가가 논의중인 것으로 알고 있습니다. 질문의 요지로 돌아와 다시 답을 드린다면, 여러분들이 Common Sense 로 생각하시기에 '이것은 안 된다'라고 생각하신다면, 규제당국 당연히 안되는 것으로 생각 할 것입니다. 그래서 혹시나 RA 를 하실 때, 업체 스스로 '이는 너무 Risk 한 것을 우리가 정당화 하는 것이 아닌가?'라는 측면에서 질문과 답을 하시다 보면, 이 부분을 해소하실 수 있을 것 같습니다.
Q3	QbD 적용이 품질 관리 측면에서 꼭 필요한 단계라는 것은 잘 인지하고 있습니다. 다만, 기 허가제품의 경우 QbD 가 적용되지 않은 제품이 많기 때문에 많은 회사에서 제조공정의 모든 파라미터를 CPP 로 설정하여 관리하고 있습니다. 이런 상황에서 기허가 제품에 대해서도 QbD 를 통한 CPP, CQA 재 설정이 필요하다고 생각하시는 지 궁금합니다.
	제 생각에는 기허가 제품이라고 한다면, QbD 를 진행하실 때 허가 자료에서 규정하는 기본적인 Tool 이나, 통계적 해석을 중점적으로 하기 보다는... 이렇게 하다 보면 시간과 비용이 굉장히 많이 소요됩니다. 그래서, 다만 기허가 제품에 대한 Requirements 는 없기 때문에 제품의 이해를 높인다는 측면에서 CPP, CQA 를 자체적으로 실행해보고, 이때는 좀 더 Optimized 된, 압축 된 스터디를 해 보시고 그 경험들이 쌓이면 제네릭 혹은 신제품 개발하실 때 적용하시면 될 것 같습니다.
Q4	경영진의 지속적인 관심 및 유도를 위해, 채용되는 툴 등이 있나요? (미팅형태로 공유는 하는데, 이후의 정규적 관심 유도가 어려운 것 같습니다.)
	저 역시 전적으로 동의합니다. 경영진 분들은 품질에 대해 아주 많은 관심을 기울이시지는 않습니다. 하지만, 또 그렇다고 아주 관심이 없으신 것은 아닙니다. 아까 잠깐 말씀드렸지만, 평소에도 쉽게 다가가실 수 있도록 Tool을 마련해 드리고, 미팅형태로 공유하신다고 하셨는데 미팅에서도 노하우를 활용해보시면 어떨까 싶습니다. 예를 들어, 30분의 미팅을 한다고 하면 경영진이 가장 관심을 가질만한 Topic을 가장 먼저 말씀하시고, 그 다음에 중요하나, 투자가 필요한 것들을 순서대로 배치한다면 꾸준하고 실직적인 미팅이 되지 않을까 싶습니다.
Q5	개발단계별로 기술이전을 해야 한다고 이해되는데, 그럼 단계별로 시험법 밸리데이션도 함께 수행해야 된다고 보면 되는 걸까요? 말씀하신 기술이전의 구체적인 범위를 알고 싶습니다.
	기술 이전의 범위는 공정과 시험법이 될 것 같습니다. 공정과 시험법 모두 개발 단계가 진행됨에 따라 optimize가 될 것이고 이에 따라 지속적인 변경(개선)이 이루어 질 것입니다. 이 과정에서 축적된 지식을 다음 단계로 transfer하는 기술이전의 주 point일 것입니다. 질문해 주신 시험법도 단계별 이전의 대상이 맞습니다. 다만, 매 단계마다 validation을 할 필요는 없을 것 같습니다. 초기 개발 단계에는 Qualification또는 Verification 수준으로 시험법이 적합한 결과를 도출할 수 있음을 증명하면 될 것 같습니다. 개발이 완료되는 즉, 개발 단계의 후반 (임상3상 또는 상업화를 위한 생산(PPQ) 진행 전)에 Method Validation을 진행하면 될 것 같습니다.

강연	연사
QbD 에 의한 의약품 허가개발의 해설과 이행방안 - Q8/9/10 Q&As (R4)	김국희

Q1	**실제적으로, 디자인스페이스를 허가자료에 포함하여 품목허가를 받은 제품은 거의 없는것으로 알고 있습니다. 그렇다면 설계공간이 필수사항이 아닐때, '의약품 개발에서 QbD 접근법을 적용했다'라고 주장하기 위해선 최소 어느 단계까지 수행해야 하는건가요?**
	설계공간이 QbD 는 아닙니다. 환자의 치료를 TPP 로 설정하고, 이하 CPP, CMA 항목들까지 Risk-based 로 근거를 만드셨다면 저는 QbD 접근법으로 개발하였다고 주장할 수 있다고 생각합니다. 사실 QbD 는 남에게 보여주기보다는, 개발과정을 보다 효율적이고 효과적으로 진행하기 위한 수단입니다. 또한 화자의 치료를 최고의 가치로 의사결정하기 위한 수단이빈다. 이를 위해서 최신의 선진적인 품질경영기법을 도입해서, 의약품 개발의 중요 가치들을 Risk-base 로 의사결정하고, 개발을 진행하는 실시간으로 허가자료의 근거가 만들어내는 QbD 접근법을 도입하는 것이지요. 만약 회사에 현재 당장 QbD 가 필요한 부분이 Process Validation 부분이라면, CPP 및 CQA 의 적용 방법만 시도해 보아도 도움이 될 수 있습니다. 개발초기라면, TPP 에서 QTPP 와 pCQA 만 QbD 접근법으로 설정해도 됩니다. 굳이 대외적으로 자랑할게 아니라면, 필요하신 해당하는 부분만 먼저 QbD 접근법을 도입하셔도 됩니다. '어디까지 해야한다'라고는 말씀드리기 어렵고, 회사에서 '개선이 필요한 부분까지만' 하시면 됩니다. 당연히 개발자료를 모두 허가 시 제출할 필요는 없습니다. 만일, CPP 나 CMA 에 대한 수치적인 근거가 필요하다면 그 부분에 대한 개발자료만 제공하시면 되고, Design Space 에 대해 규제 유연성을 요구하겠다고 하면 '이렇게 운영했을 때 품질이 더 일정합니다'에 대한 자료만 제공하시면 된다고 생각합니다. 하지만 남에게 보여지는 부분에 치중하는 QbD 활동에 대해서, 제가 걱정되는 건, 허가자료에 주로 보여지는 공정에 대한 근거만 QbD 를 도입하시면 공정은 조금 더 재현성이 높아졌지만, 환자에게 더 필요한 품질의 관점과 먼 지점에서 재현성만 좋아지는 것일 수도 있는 것입니다. QbD 를 하는 목적은 "환자의 치료"에 더 적합한 의약품을 만드는 것입니다. 저는 그래서 남들에게 잘 보여지지 않는 부분인 TPP 에서 QTPP 로 설정하는 활동을 QbD 접근법으로 하는 것이 더 중요하다고 생각합니다.
Q2	**원하는 수준의 공정에 대한 이해 만큼의 CPP 를 설정하여 근거를 제시하는 것을 추천하셨는데, 이에 대해 규제당국이 받아들일 수 있는지 궁금합니다. 가령 A 라는 공정에 대해 회사 내 사전 지식 및 경험등을 통해 non-CPP 로 분류하였지만 규제당국에서는 이를 받아들이지 않을 경우, 어떤 식으로 대응하는게 바람직할까요?**
	규제당국도 이전의 경험의 잣대로 허가자료를 검토합니다. 그러다 보니, 가이드라인에서 추천 되었거나, 이전 다른 회사에서 CPP 로 설정한 항목을 non-CPP 로 분류하였다면, 그에 대해서 의문을 제시할 수 있습니다. 하지만 근거를 제시하고 설득하면 불가능하지는 않습니다. 그리고 제 경험상으로 충분히 근거가 있는 CPP 설정에 규제당국이 끝까지 우기는 것은 보지 못했습니다. 결국은 규제기관을 설득할 수 있냐도 중요합니다. 허가 과정은 "대화"입니다. 규제 당국이 왜 그렇게 주장하는지를 듣는 것이 중요할 수 있습니다. QbD 접근법으로 착실히 자료가 만들어져 있다면, 충분히 설득이 가능할 꺼라고 생각합니다. 하지만 규제당국에서 지속적으로 요구한다면 이유가 있을 것입니다. 규제적으로 CPP 로 설정해야 항목들일 수도 있습니다. 그리고 개발사에서 만든 "그 원하는 수준의 공정 이해"가 부족한 것일 수 있습니다. 품질의 일관성을 유지할 수 있는 충분한 지식을 토대로 CPP 를 설정하셔야 합니다. 저는 품질의 일관성을 유지하기 위한 해법은 다양할 수 있다는 것을 말씀드렸습니다. 규제당국에서 CPP 설정을 끝까지 요구한다면, 분명 이유가 있을 것입니다. 규제당국이 왜 CPP 라고 생각하는지 물어보시고, 이에 대해 답을 해주시는게 좋을 것 같습니다. 규제당국을 설득할 수 없다면, 그 근거가 부족한 것이므로, 규제당국의 주장을 받아들여서 CPP 로 추가하는 것이 해결책입니다.
Q3	**개발단계별로 기술이전을 해야 한다고 이해되는데, 그럼 단계별로 시험법 밸리데이션도 함께 수행해야 된다고 보면 되는 걸까요? 기술이전의 구체적인 범위를 알고 싶습니다.**
	시험법 밸리데이션은 최초에 한번 진행하시고, 변경이 생길 때마다 추가 밸리데이션만 진행하시면 됩니다. 개발단계별로 매번 기술이전을 하실 필요는 없습니다. 변경에 대해서 잘 관리하시고, 그 변경따라 필요한 활동을 하시면 됩니다. 시험법 밸리데이션에 대해서는 ICH Q2 와 규제기관의 가이드라인을 참고하시기 바랍니다.

Q8/9/10 Q&As -
QbD에 의한 의약품 허가개발의 해설과 이행방안

(김국희/오송첨단의료산업진흥재단)

강연 질의 Q3. 보충자료

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Annex 7

WHO guidelines on transfer of technology in pharmaceutical manufacturing

1. Introduction
2. Scope
3. Glossary
4. Organization and management
5. Production: transfer (processing, packaging and cleaning)
6. Quality control: analytical method transfer
7. Premises and equipment
8. Documentation
9. Qualification and validation

References

1. Introduction

These guiding principles on transfer of technology are intended to serve as a framework which can be applied in a flexible manner rather than as strict rigid guidance. Focus has been placed on the quality aspects, in line with WHO's mandate.

1.1 Transfer of processes to an alternative site occurs at some stage in the life-cycle of most products, from development, scale-up, manufacturing, production and launch, to the post-approval phase.

1.2 Transfer of technology is defined as "a logical procedure that controls the transfer of any process together with its documentation and professional expertise between development and manufacture or between manufacture sites". It is a systematic procedure that is followed in order to pass the documented knowledge and experience gained during development and or commercialization to an appropriate, responsible and authorized party. Technology transfer embodies both the transfer of documentation and the demonstrated ability of the receiving unit (RU) to effectively perform the critical elements of the transferred technology, to the satisfaction of all parties and any applicable regulatory bodies.

1.3 Literature searches revealed little information on the subject originating from national or regional regulatory bodies. Guidance on intracompany transfers was prepared by the International Society for Pharmaceutical Engineering (ISPE) (*1*).

1.4 The ever changing business strategies of pharmaceutical companies increasingly involve intra- and intercompany transfers of technology for reasons such as the need for additional capacity, relocation of operations or consolidations and mergers. The WHO Expert Committee on Specifications for Pharmaceutical Preparations, therefore, recommended in its forty-second report that WHO address this issue through preparation of WHO guidelines on this matter (*2*).

1.5 Transfer of technology requires a documented, planned approach using trained and knowledgeable personnel working within a quality system, with documentation of data covering all aspects of development, production and quality control. Usually there is a sending unit (SU), a receiving unit and the unit managing the process, which may or may not be a separate entity. For "contract manufacturing" please see good manufacturing practices (GMP) (*3*).

1.6 For the transfer to be successful, the following general principles and requirements should be met:

- the project plan should encompass the quality aspects of the project and be based upon the principles of quality risk management;

- the capabilities of the SU and at the RU should be similar, but not necessarily identical, and facilities and equipment should operate according to similar operating principles;
- a comprehensive technical gap analysis between the SU and RU including technical risk assessment and potential regulatory gaps, should be performed as needed;
- adequately trained staff should be available or should be trained at the RU:
  — regulatory requirements in the countries of the SU and the RU, and in any countries where the product is intended to be supplied, should be taken into account and interpreted consistently throughout any transfer programme project; and
  — there should be effective process and product knowledge transfer.

1.7 Technology transfer can be considered successful if there is documented evidence that the RU can routinely reproduce the transferred product, process or method against a predefined set of specifications as agreed with the SU.

1.8 In the event that the RU identifies particular problems with the process during the transfer, the RU should communicate them back to the SU to ensure continuing knowledge management.

1.9 Technology transfer projects, particularly those between different companies, have legal and economic implications. If such issues, which may include intellectual property rights, royalties, pricing, conflict of interest and confidentiality, are expected to impact on open communication of technical matters in any way, they should be addressed before and during planning and execution of the transfer.

1.10 Any lack of transparency may lead to ineffective transfer of technology.

1.11 Some of the principles outlined in this document may also be applicable to manufacturing investigational pharmaceutical products for clinical trials as part of research and development, but this is not the main focus of this guidance and has been excluded due to the complexity of the processes.

1.12 Some of the responsibilities outlined in this document for the SU may also be considered to be part of the management unit responsibilities.

2. Scope

Note: This section specifically provides for transfer of quality control (QC) methods where a technical agreement exists (SU manufacturer to RU manufacturer or SU manufacturer to RU QC laboratory). Where no such technical agreements exist (e.g. testing by national laboratories or testing

for procurement agencies) a number of the points listed in section 2.4 may not be workable, and alternative approaches may be required.

2.1 This document gives guidance in principle and provides general recommendations on the activities necessary to conduct a successful intra- or intersite transfer of technology as described in the Introduction to these guidelines. The intention is to address the basic considerations needed for a successful transfer in order to satisfy the regulatory authority defined for the transfer process.

2.2 The guidelines will be applied to manufacturing active pharmaceutical ingredients (APIs), manufacturing and packaging of bulk materials, manufacturing and packaging of finished pharmaceutical products (FPPs) and/or performing analytical testing.

2.3 The recommendations provided in these guidelines apply to all dosage forms but need to be adjusted on a case-by-case basis (e.g. by using risk management principles). Particularly close control of certain aspects will be required for certain formulations such as sterile products, and metered-dose aerosols. WHO guidance on manufacture of specific pharmaceutical products *(4,5)* will be useful in this regard.

2.4 The guidelines address the following areas at the SU and the RU:

— transfer of development and production (processing, packaging and cleaning);
— transfer of analytical methods for quality assurance and quality control;
— skills assessment and training;
— organization and management of the transfer;
— assessment of premises and equipment;
— documentation; and
— qualification and validation.

2.5 Because each transfer project is unique, the provision of a comprehensive set of guidelines is beyond the scope of this document.

2.6 These guidelines do not provide guidance on any legal, financial or commercial considerations associated with technology transfer projects.

3. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

acceptance criteria

Measurable terms under which a test result will be considered acceptable.

active pharmaceutical ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

bracketing

An experimental design to test only the extremes of, for example, dosage strength. The design assumes that the extremes will be representative of all the samples between the extremes.

change control (C/C)

A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status. The intent is to determine the need for action that would ensure that the system is maintained in a validated state.

commissioning

The setting up, adjustment and testing of equipment or a system to ensure that it meets all the requirements, as specified in the user requirement specification, and capacities as specified by the designer or developer. Commissioning is carried out before qualification and validation.

control strategy

A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related tomaterials and components related to drug substances and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control (*6*).

corrective action (C/A)

Any action to be taken when the results of monitoring at a critical control point indicate a loss of control.

critical

Having the potential to impact on product quality or performance in a significant way.

critical control point (CCP)

A step at which control can be applied and is essential to prevent or eliminate a pharmaceutical quality hazard or to reduce it to an acceptable level.

design qualification (DQ)

Documented evidence that the premises, supporting systems, utilities, equipment and processes have been designed in accordance with the requirements of good manufacturing practices (GMP).

design space

The multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality (*7*).

drug master file (DMF)

Detailed information concerning a specific facility, process or product submitted to the medicines regulatory authority, intended for incorporation into the application for marketing authorization.

finished pharmaceutical product (FPP)

A product that has undergone all stages of production, including packaging in its final container and labelling. An FPP may contain one or more APIs.

gap analysis

Identification of critical elements of a process which are available at the SU but are missing from the RU.

good manufacturing practices (GMP)

That part of quality assurance which ensures that pharmaceutical products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization (*3*).

in-process control (IPC)

Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

installation qualification (IQ)

The performance of tests to ensure that the installations (such as machines, measuring devices, utilities and manufacturing areas) used in a manufacturing process are appropriately selected and correctly installed and operate in accordance with established specifications.

intercompany transfer

A transfer of technology between sites of different companies.

intracompany transfer

A transfer of technology between sites of the same group of companies.

operational qualification (OQ)

Documented verification that the system or subsystem performs as intended over all anticipated operating ranges.

performance qualification (PQ)

Documented verification that the equipment or system operates consistently and gives reproducibility within defined specifications and parameters for prolonged periods. (In the context of systems, the term "process validation" may also be used.)

process validation

Documented evidence which provides a high degree of assurance that a specific process will consistently result in a product that meets its predetermined specifications and quality characteristics.

qualification

Action of proving and documenting that any premises, systems and equipment are properly installed, and/or work correctly and lead to the expected results. Qualification is often a part (the initial stage) of validation, but the individual qualification steps alone do not constitute process validation.

qualification batches

Those batches produced by the RU to demonstrate its ability to reproduce the product *(1)*.

quality assurance (QA)

Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the objective of ensuring that pharmaceutical products are of the quality required for their intended use.

quality control (QC)

Quality control covers all measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that starting materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics.

quality planning

Part of quality management focused on setting quality objectives and specifying necessary operational processes and related resources to fulfil the quality objectives *(6)*.

quality policy

Overall intentions and direction of an organization related to quality as formally expressed by senior management *(6)*.

quality risk management (QRM)

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the pharmaceutical product throughout the product life-cycle.

receiving unit (RU)

The involved disciplines at an organization where a designated product, process or method is expected to be transferred.

sending unit (SU)

The involved disciplines at an organization from where a designated product, process or method is expected to be transferred.

spiking

The addition of a known amount of a compound to a standard, sample or placebo, typically for the purpose of confirming the performance of an analytical procedure.

standard operating procedure (SOP)

An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g. equipment operation, maintenance and cleaning, validation, cleaning of premises and environmental control, sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

technology transfer report

A documented summary of a specific technology transfer project listing procedures, acceptance criteria, results achieved and conclusions. Any deviation should be discussed and justified.

validation

Action of proving and documenting that any process, procedure or method actually and consistently leads to the expected results.

validation master plan (VMP)

A high-level document that establishes an umbrella validation plan for the entire project and summarizes the manufacturer's overall philosophy and approach, to be used for establishing performance adequacy. It provides information on the manufacturer's validation work programme and defines details of and timescales for the validation work to be performed, including a statement of the responsibilities of those implementing the plan.

validation protocol (or plan) (VP)

A document describing the activities to be performed in a validation, including the acceptance criteria for the approval of a manufacturing process — or a part thereof — for routine use.

validation report (VR)

A document in which the records, results and evaluation of a completed validation programme are assembled and summarized. It may also contain proposals for the improvement of processes and or equipment.

4. Organization and management

4.1 Transfer comprises an SU and an RU. In some circumstances there may be an additional unit which will be responsible for directing, managing and approving the transfer.

4.2 There is a formal agreement between the parties, which specifies the responsibilities before, during and after transfer.

4.3 Organization and management of a successful technology transfer need to ensure that the main steps have been executed and documented as described in section 1.6.

4.4 There should be a project management plan which identifies and controls all the necessary activities identified at the start of the undertaking.

4.5 The transfer protocol should list the intended sequential stages of the transfer. The protocol should include:

— objective;
— scope;
— key personnel and their responsibilities;
— a parallel comparison of materials, methods and equipment;
— the transfer stages with documented evidence that each critical stage has been satisfactorily accomplished before the next commences;
— identification of critical control points;
— experimental design and acceptance criteria for analytical methods;
— information on trial production batches, qualification batches and process validation;
— change control for any process deviations encountered;
— assessment of end-product;
— arrangements for keeping retention samples of active ingredients, intermediates and finished products, and information on reference substances where applicable; and
— conclusion, including signed-off approval by project manager.

4.6 The SU should provide the necessary validation documentation for the process and its support functions. Usually, an established process is transferred, and such documentation is already available.

4.7 The SU should provide criteria and information on hazards and critical steps associated with the product, process or method to be transferred, to serve as a basis for a quality risk management (QRM) exercise at the RU (*7–10*).

4.8 The SU or third party should assess the suitability and degree of preparedness of the RU before transfer, with regard to premises, equipment and support services (e.g. purchasing and inventory control mechanisms, quality control (QC) procedures, documentation, computer validation, site validation, equipment qualification, water for pharmaceutical production and waste management).

4.9 The SU and the RU should jointly verify that the following, satisfactorily completed, validation protocols are available:

- installation qualification (IQ) and operational qualification (OQ) data for manufacturing and packaging equipment at the RU site and analytical equipment; and
- qualification of the rooms for both manufacture and packaging at the RU site.

4.10 The SU and the RU should jointly implement any training programmes that may be required specific to the product, process or method to be transferred, e.g. on analytical methods or equipment usage, and assess training outcomes.

4.11 The SU and the RU should jointly execute the transfer protocol according to a checklist and or flow diagram showing the sequence of steps to be carried out to effect an efficient transfer.

4.12 Any changes and adaptations made during the course of the technology transfer should be fully documented.

4.13 The SU and the RU should jointly document the execution of the transfer protocol in a transfer of technology summary in a report.

Project team

4.14 Any transfer project will be managed by a team comprising members with clearly defined key responsibilities. The team should be drawn from members of relevant disciplines from both the SU and RU sites.

4.15 The team members should have the necessary qualifications and experience to manage their particular aspect of the transfer.

5. Production: transfer (processing, packaging and cleaning)

5.1 The RU should be able to accommodate the intended production capacity. If possible, it should be established at the outset whether the intention is to perform single-batch manufacture, continuous production or campaigns.

5.2 Consideration should be given to the level and depth of detail to be transferred to support production and any further process development and optimization at the RU as intended under the transfer project plan.

5.3 Consideration should be given to the technical expertise, site technology and site capabilities for the RU. It should be identified upfront by the SU of any process robustness issues so that plans may be put in place at the RU.

5.4 The SU and the RU should jointly develop a protocol for the transfer of relevant information related to the process under consideration from the SU to the RU, as well as the development of a comparable process at the RU.

Starting materials

5.5 The specifications and relevant functional characteristics of the starting materials (APIs and excipients) (*11,12*) to be used at the RU should be consistent with materials used at the SU. Any properties which are likely to influence the process or product should be identified and characterized.

Active pharmaceutical ingredients (API)

5.6 The SU should provide the RU with the open (applicant's) part of the API master file (APIMF or drug master file (DMF) or active substance master file (ASMF)), or equivalent information and any relevant additional information on the API of importance for the manufacture of the pharmaceutical product. The following are examples of the information which may typically be provided; however the information needed in each specific case should be assessed using the principles of QRM:

- manufacturer and associated supply chain;
- step of the API to be transferred;
- flow chart of synthesis pathway, outlining the process, including entry points for raw materials, critical steps, process controls and intermediates;
- where relevant, definitive physical form of the API (including photomicrographs and other relevant data) and any polymorphic and solvate forms;
- solubility profile;

- if relevant, pH in solution;
- partition coefficient, including the method of determination;
- intrinsic dissolution rate, including the method of determination;
- particle size and distribution, including the method of determination;
- bulk physical properties, including data on bulk and tap density, surface area and porosity as appropriate;
- water content and determination of hygroscopicity, including water activity data and special handling requirements;
- microbiological considerations (including sterility, bacterial endotoxins and bioburden levels where the API supports microbiological growth) in accordance with national, regional or international pharmacopoeial requirements;
- specifications and justification for release and end-of-life limits;
- summary of stability studies conducted in conformity with current guidelines, including conclusions and recommendations on retest date;
- list of potential and observed synthetic impurities, with data to support proposed specifications and typically observed levels;
- information on degradants, with a list of potential and observed degradation products and data to support proposed specifications and typically observed levels;
- potency factor, indicating observed purity and justification for any recommended adjustment to the input quantity of API for product manufacturing, providing example calculations; and
- special considerations with implications for storage and or handling, including but not limited to safety and environmental factors (e.g. as specified in material safety data sheets) and sensitivity to heat, light or moisture.

Excipients

5.7 The excipients (*11*) to be used have a potential impact on the final product. Their specifications and relevant functional characteristics should, therefore, be made available by the SU for transfer to the RU site. The following are examples of the information which may typically be provided; however, the information needed in each specific case should be assessed using the principles of QRM:

- manufacturer and associated supply chain;
- description of functionality, with justification for inclusion of any antioxidant, preservative or any excipient;
- definitive form (particularly for solid and inhaled dosage forms);
- solubility profile (particularly for inhaled and transdermal dosage forms);
- partition coefficient, including the method of determination (for transdermal dosage forms);

- intrinsic dissolution rate, including the method of determination (for transdermal dosage forms);
- particle size and distribution, including the method of determination (for solid, inhaled and transdermal dosage forms);
- bulk physical properties, including data on bulk and tap density, surface area and porosity as appropriate (for solid and inhaled dosage forms);
- compaction properties (for solid dosage forms);
- melting point range (for semi-solid or topical dosage forms);
- pH range (for parenteral, semi-solid or topical, liquid and transdermal dosage forms);
- ionic strength (for parenteral dosage forms);
- specific density or gravity (for parenteral, semi-solid or topical, liquid and transdermal dosage forms);
- viscosity and or viscoelasticity (for parenteral, semi-solid or topical, liquid and transdermal dosage forms);
- osmolarity (for parenteral dosage forms);
- water content and determination of hygroscopicity, including water activity data and special handling requirements (for solid and inhaled dosage forms);
- moisture content range (for parenteral, semisolid or topical, liquid and transdermal dosage forms);
- microbiological considerations (including sterility, bacterial endotoxins and bioburden levels where the excipient supports microbiological growth) in accordance with national, regional or international pharmacopoeial requirements, as applicable (for general and specific monographs);
- specifications and justification for release and end-of-life limits;
- information on adhesives supporting compliance with peel, sheer and adhesion design criteria (for transdermal dosage forms);
- special considerations with implications for storage and or handling, including but not limited to safety and environmental factors (e.g. as specified in material safety data sheets (MSDS)) and sensitivity to heat, light or moisture; and
- regulatory considerations, e.g. documentation to support compliance with transmissible animal spongiform encephalopathy certification requirements (where applicable).

Information on process and finished pharmaceutical products information

5.8 The SU should provide a detailed characterization of the product, including its qualitative and quantitative composition, physical description, method of manufacture, in-process controls, control method and specifications, packaging components and configurations, and any safety and handling considerations.

5.9 The SU should provide any information on the history of process development which may be required to enable the RU to perform any further development and or process optimization after successful transfer. Such information may include the following:

- information on clinical development, e.g. information on the rationale for the synthesis, route and form selection, technology selection, equipment, clinical tests, and product composition;
- information on scale-up activities: process optimization, statistical optimization of critical process parameters, critical quality attributes, pilot report and or information on pilot-scale development activities indicating the number and disposition of batches manufactured;
- information or report on full-scale development activities, indicating the number and disposition of batches manufactured, and deviation and change control (sometimes referred to as change management) reports which led to the current manufacturing process;
- the change history and reasons, e.g. a change control log, indicating any changes to the process or primary packaging or analytical methods as a part of process optimization or improvement; and
- information on investigations of problems and the outcomes of the investigations.

5.10 The SU should provide to the RU information on any health, safety and environmental issues associated with the manufacturing processes to be transferred, and the implications, e.g. need for gowning or protective clothing.

5.11 The SU should provide to the RU information on current processing and testing, including but not limited to:

- a detailed description of facility requirements and equipment;
- information on starting materials, applicable MSDS and storage requirements for raw materials and finished products;
- description of manufacturing steps (narrative and process maps or flow charts, and or master batch records), including qualification of in-processing hold times and conditions, order and method of raw material addition and bulk transfers between processing steps;
- description of analytical methods;
- identification and justification of control strategy (e.g. identification of critical performance aspects for specific dosage forms, identification of process control points, product quality attributes and qualification of critical processing parameter ranges, statistical process control (SPC) charts);
- design space, in cases where this has been defined;
- validation information, e.g. validation plans and reports;
- annual product quality reviews;

- stability information;
- an authorized set of protocols and work instructions for manufacturing; and
- environmental conditions or any special requirement needed for the facility or equipment depending on the nature of the product to be transferred.

5.12 During the transfer process, the RU should identify any differences in facilities, systems and capabilities and communicate with the SU about these differences to understand the potential impact on ability to run the process to deliver good product quality. Differences should be understood and satisfactorily addressed to assure equivalent product quality. Based on the information received from the SU, the RU should consider its own capability to manufacture and pack the product to the required standards and should develop relevant plant operating procedures and documentation before the start of production. Process development at the RU should address the following tasks:

- comparison and assessment of suitability and qualification of facility and equipment;
- description of manufacturing process and flow of personnel and of materials at the RU (narrative and or process maps or flow charts);
- determination of critical steps in manufacture, including hold times, end-points, sampling points and sampling techniques (*13*);
- writing and approval of SOPs for all production operations (e.g. dispensing, granulation or blending or solution preparation, tablet compression, tablet coating, encapsulation, liquid filling, primary and secondary packaging and in-process quality control), packaging, cleaning, testing and storage;
- evaluation of stability information, with generation of site-specific stability data if required (*14*); and
- compliance with regulatory requirements for any changes made, e.g. in terms of batch size.

Packaging

5.13 The transfer of packaging operations should follow the same procedural patterns as those of the production transfer.

5.14 Information on packaging to be transferred from the SU to the RU includes specifications for a suitable container or closure system, as well as any relevant additional information on design, packing, processing or labelling requirements and tamper-evident and anti-counterfeiting measures needed for qualification of packaging components at the RU.

5.15 For QC testing of packaging components, specifications should be provided for drawings, artwork and material (for example, glass, card or fibre board).

5.16 Based on the information provided, the RU should perform a suitability study for initial qualification of the packaging components. Packaging is considered suitable if it provides adequate protection (preventing degradation of the medicinedue to environmental influences), safety (absence of undesirable substances released into the product), compatibility (absence of interaction possibly affecting medicine quality) and performance (functionality in terms of drug delivery).

Cleaning

5.17 During the manufacturing process, pharmaceutical products and APIs can be contaminated by other pharmaceutical products or APIs if the plant is processing different products. To minimize the risk of contamination and cross-contamination, operator exposure and environmental effects, adequate cleaning procedures are essential.

5.18 Cleaning procedures and their validation are site-specific. In order for the RU to define its cleaning strategy the SU should provide information on cleaning at the SU to minimize cross-contamination due to residues from previous manufacturing steps, operator exposure and environmental impact, including:

— information on solubility of active ingredients, excipients and vehicles;
— minimum therapeutic doses of active ingredients;
— therapeutic category and toxicological assessment; and
— existing cleaning procedures.

Additional information should be provided, as appropriate and where available, e.g.:

— cleaning validation reports (chemical and microbiological);
— information on cleaning agents used (efficacy, evidence that they do not interfere with analytical testing for residues of APIs, removal of residual cleaning agents); and
— recovery studies to validate the sampling methodology.

5.19 Before the transfer, the SU should provide information on limits for product residues, and the rationale for limit selection.

5.20 Based on the information provided by the SU, cleaning procedures should be designed at the RU, taking into account relevant characteristics of the starting materials (e.g. potency, toxicity, solubility, corrosiveness and temperature sensitivity), manufacturing equipment design and configuration, cleaning agent and products residue.

Implementation of processing, packaging and cleaning systems

5.21 Trial batch(es) ("demonstration batches") are normally produced to confirm process capability before initiating formal validation. Where trial

batches are produced, at a minimum, all critical processing parameters and finished product specifications should be assessed.

5.22 Once process capability has been established at the RU, assuring that the product, process or method at the RU meets predefined and justified specifications, process validation and cleaning validation can be carried out.

6. Quality control: analytical method transfer

6.1 Transfer of analytical methods should accommodate all the analytical testing required to demonstrate compliance of the product to be transferred with the registered specification (*15*).

6.2 Analytical methods used to test pharmaceutical products, starting materials, packaging components and cleaning (residue) samples, if applicable, should be implemented at the testing laboratory before testing of samples for process validation studies is performed by the RU. Process validation samples may be tested at the RU, the SU or a third laboratory.

6.3 A protocol defining the steps should be prepared for transfer of analytical methods. The analytical methods transfer protocol should include a description of the objective, scope and responsibilities of the SU and the RU; a specification of materials and methods; the experimental design and acceptance criteria; documentation (including information to be supplied with the results, and report forms to be used, if any); procedure for the handling of deviations; references; signed approval; and details of reference samples (starting materials, intermediates and finished products).

6.4 The SU's responsibilities for the transfer of analytical methods are to:

- provide method-specific training for analysts and other quality control staff, if required;
- assist in analysis of QC testing results;
- define all methods to be transferred for testing a given product, starting material or cleaning sample;
- define experimental design, sampling methods and acceptance criteria;
- provide any validation reports for methods under transfer and demonstrate their robustness;
- provide details of the equipment used, as necessary (part of validation report, if available) and any standard reference samples;
- provide approved procedures used in testing; and
- review and approve transfer reports.

6.5 The RU's responsibilities are to:

- review analytical methods provided by the SU, and formally agree on acceptance criteria before execution of the transfer protocol;

- ensure that the necessary equipment for QC is available and qualified at the RU site. The equipment used by the RU during the analytical transfer should meet appropriate specifications to ensure the requirements of the method or specification are met;
- ensure that adequately trained and experienced personnel are in place for analytical testing;
- provide a documentation system capable of recording receipt and testing of samples to the required specification using approved test methods, and of reporting, recording and collating data and designation of status (approved, rejected, quarantine);
- execute the transfer protocol;
- perform the appropriate level of validation to support the implementation of the methods; and
- generate and obtain approval of transfer reports.

6.6 Appropriate training should be provided and all training activities and outcomes should be documented.

6.7 Reference to compendial monographs (e.g. *The International Pharmacopoeia* (*15*), *European Pharmacopoeia*, *British Pharmacopoeia* and *United States Pharmacopeia*), where available, is expected.

6.8 Possible experimental designs and acceptance criteria for the main analytical testing methods are shown in Table 1. Note that this table represents high-level guidance to apply the general principle that method transfers should account for the variability and sensitivity of the method and the specifications for the quality parameter. Alternative procedures and acceptance criteria may be applied based on science and the characteristics of the analytical method and the analyte.

Table 1
Possible experimental designs and acceptance criteria for analytical testing

Test	Considerations for transfer	Replication of tests	Set-up	Acceptance criteria	
				Direct	Statistically derived
Identity	Transfer should focus on sample preparation, instruments, data interpretation. Acceptable to include in assay transfer where relevant	One determination usually sufficient to demonstrate equivalence			

Test	Considerations for transfer	Replication of tests	Set-up	Acceptance criteria	
				Direct	Statistically derived
Assay for potency	– *Non-specific assay should not be used for stability testing.* – Bracketing may be appropriate for multiple strengths	At each site: 2 analysts × 3 lots, in triplicate (= 18 per site)	Different sets of instruments and columns Independent solution preparation	Comparison of mean and variability	Two one-sided *t*-tests with intersite differences ≤ 2% , 95% confidence
Content uniformity	If method is equivalent to assay method, separate transfer is not usually requird	At each site: 2 analysts, × 1 lot (= 2 per site)	Different sets of instruments and columns Independent solution preparation	Mean at RU within ± 3% of mean at SU; comparison of relative st. dev.	Two one-sided *t*-tests with intersite differences ≤ 3% , 95% confidence
Dissolution	Bracketing may be appropriate for multiple strengths	6 units (12 if not routine at RU, and for extended release products)		Mean at RU within ± 5% of mean at SU	Compare profile (e.g. F^2), or Compare data at Q time points as for assay
Cleaning verification (recovery of residues from surfaces)	Confirm that same swabbing material is used at sending unit (SU) and receiving unit (RU)		Use spiked samples, with levels within 3× validated st. dev. or within ± 10% of specification (whichever is the greater)	– All samples spiked above specification should fail – 90% of samples spiked below specification should pass	
Microbiological testing (qualitative and quantitative limit tests)	– Execute common on-site validation protocol: rationale; method identity; validation parameters; data summary; acceptance criteria; methods of compiling and analysing data; handling of out-of-specification results; follow-up requirements – Use same materials, techniques, inoculum preparation	Validation in triplicate	Use different lots for each validation exercise	– Qualitative: Demonstrate recovery of microorganisms – Quantitative: Recovery levels within acceptance limits specified in protocol	

Test	Considerations for transfer	Replication of tests	Set-up	Acceptance criteria	
				Direct	Statistically derived
Impurity, degradation, residual solvents	– Confirm response factors for calculation relative to drug peak; – Confirm limit of quantitation at RU; – Compare chromatograms – Compare accuracy and precision for spiking experiments	At each site: 2 analysts × 3 lots, in duplicate (in triplicate if done together with assay)	– Different days, different sets of instruments and columns – Use samples of similar age, homogeneity, packaging, storage – Use spiked samples if necessary	(For low levels) Values at RU within ± 25% of values at SU, or Mean at RU within ± 0.05% of mean at SU (5%)	(For moderately high levels) Two one-sided *t*-tests, differences ≤ 10%, 95% confidence

st. dev., standard deviation.
Note: numbers in the table are given as examples only and should not be considered as recommendations.

The SU and the RU should execute the transfer protocol and jointly prepare a transfer report. The points to be addressed in the analytical methods transfer report are listed in these guidelines.

7. Premises and equipment

Premises

7.1 The SU should provide information to the RU on the layout, construction and finish of buildings and services (*16*,*17*) (heating, ventilation and air-conditioning (HVAC), temperature, relative humidity, water, power, and compressed air), which have an impact on the product, process or method to be transferred.

7.2 The SU should provide information on relevant health, safety and environmental issues, including:

- inherent risks of the manufacturing processes (e.g. reactive chemical hazards, exposure limits, fire and explosion risks);
- health and safety requirements to minimize operator exposure (e.g. atmospheric containment of pharmaceutical dust);
- emergency planning considerations (e.g. in case of gas or dust release, spillage, fire and firewater run-off); and
- identification of waste streams and provisions for re-use, recycling and/or disposal.

Equipment

7.3 The SU should provide a list of equipment, makes and models involved in the manufacture, filling, packing and or control of the product, process or method to be transferred, together with existing qualification and validation documentation. Relevant documentation may include:

— drawings;
— manuals;
— maintenance logs;
— calibration logs; and
— procedures (e.g. regarding equipment set-up, operation, cleaning, maintenance, calibration and storage).

7.4 The RU should review the information provided by the SU together with its own inventory list including the qualification status (IQ, OQ, PQ) of all equipment and systems, and perform a side-by-side comparison of equipment at the two sites in terms of their functionality, makes, models and qualification status.

7.5 The RU should perform a gap analysis to identify requirements for adaptation of existing equipment, or acquisition of new equipment, or a change in the process, to enable the RU to reproduce the process being transferred. GMP requirements should be satisfied and intended production volumes and batch sizes (e.g. same, scaled-up or campaign) should be considered. Factors to be compared include:

— minimum and maximum capacity;
— material of construction;
— critical operating parameters;
— critical equipment components (e.g. filters, screens, and temperature/pressure sensors);
— critical quality attribute; and
— range of intended use.

7.6 The facility- and building-specific location of all equipment at the RU should be considered at the time of drawing up process maps or flow charts of the manufacturing process to be transferred, including flows of personnel and material.

7.7 The impact of manufacturing new products on products currently manufactured with the same equipment should be determined.

7.8 Any modification of existing equipment that needs to be adapted to become capable of reproducing the process being transferred should be documented in the transfer project plan.

8. Documentation

8.1 The documentation required for the transfer project itself is wide-ranging. Examples of documentation commonly required are summarized in Table 2.

8.2 The documented evidence that the transfer of technology has been considered successful should be formalized and stated in a technology transfer summary report. That report should summarize the scope of the transfer, the critical parameters as obtained in the SU and RU (preferably in a tabulated format) and the final conclusions of the transfer. Possible discrepancies should be listed and appropriate actions, where needed, taken to resolve them.

Table 2
Examples of documentation for transfer of technology (TOT)

Key task	Documentation provided by SU	Transfer documentation
Project definition	Project plan and quality plan (where separate documents), protocol, risk assessments, gap analysis	Project implementation plan **TOT protocol**
Quality agreement		
Facility assessment	Plans and layout of facility, buildings (construction, finish) Qualification status (DQ, IQ, OQ) and reports	Side-by-side comparison with RU facility and buildings; gap analysis **Qualification protocol and report**
Health & Safety assessment	Product-specific waste management plans Contingency plans	
Skill set analysis and training	SOPs and training documentation (product-specific operations, analysis, testing)	Training protocols, assessment results
Analytical method transfer	Analytical method specifications and validation, including in-process quality control	Analytical methods transfer protocol and report
Starting material evaluation	Specifications and additional information on APIs, excipients	

Key task	Documentation provided by SU	Transfer documentation
Equipment selection and transfer	Inventory list of all equipment and systems, including makes, models, qualification status (IQ, OQ, PQ) Drawings, manuals, logs, SOPs (e.g. set-up, operation, cleaning, maintenance, calibration, storage)	Side-by-side comparison with RU equipment (makes, models, qualification status) Gap analysis **Qualification and validation protocol and report**
Process transfer: manufacturing and packaging	Reference batches (clinical, dossier, biobatches) Development report (manufacturing process rationale) History of critical analytical data Rationale for specifications Change control documentation Critical manufacturing process parameters Process validation reports Drug master file API validation status and report(s) Product stability data Current master batch manufacturing and packaging records List of all batches produced Deviation reports Investigations, complaints, recalls Annual product review	History of process development at RU Experiences at RU should be recorded for future reference Provisional batch manufacturing document (RU to develop) Provisional batch packaging document (RU to develop) Description of process at RU (narrative, process map, flow chart) **Process validation protocol and report**
Cleaning	Cleaning validation, including: Solubility information; therapeutic doses; category (toxicology); existing cleaning SOPs; validation reports — chemical and micro; agents used; recovery study	Product- and site-specific cleaning SOPs at RU **Cleaning validation protocol and report**

DQ, design qualification; IQ, installation qualification; OQ, operational qualification; API, active pharmaceutical ingredient; SOPs, standard operating procedures; RU, receiving unit.

9. Qualification and validation

General

9.1 The extent of qualification and or validation (*18*) to be performed should be determined on the basis of risk management principles.

9.2 Qualification and validation should be documented.

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