A concern in using OV is the potential to expose others. Assessment of viral shedding in animals will aid in the clinical monitoring plan. OV shedding information can be used to guide monitoring for long-term adverse effects in both non-clinical and clinical studies.

3.6 Toxicology and safety studies

The biodistribution and persistence profile of the OV and the expression profile of the transgene (if present) often guide the duration of the toxicology studies and the time intervals selected for sacrifice of animals. The toxicology assessment of an OV should be comprehensive enough to identify, characterize and quantify potential local and systemic toxicities following administration. The animal species, the route and procedure for product administration, the potentially therapeutic dose range and the dosing schedule, established from proof of concept studies, should guide the design of the toxicology studies. Since toxicity can be dependent on the route of administration of the OV, the route and the dosing schedule should mimic the intended clinical scenario as closely as possible. Outcomes measured include acute and chronic toxicities, reversibility of toxicities, delayed toxicities, and any dose-response effects. While certain aspects of the overall scientific principles of the ICH S6 guideline entitled, *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*[1], are applicable, the toxicology testing will need to reflect the biological characteristics of the OV, including the potential for viral replication and infectivity in normal cells/tissue and an undesired immune response to the virus and/or the expressed transgene.

3.7 Good Laboratory Practice (GLP) Studies

Safety endpoints are often collected in studies conducted using tumour-bearing animals, which can result in unique animal care situations. Full compliance with GLP, where required by regional law, can be difficult. Biosafety requirements can also impact the ability to conduct a non-clinical study with an OV in full compliance with GLP. Non-GLP studies might therefore be appropriate as long as they are performed in accordance with a prospectively designed protocol and the data are of sufficient quality and integrity to support the proposed clinical trial.

4. Clinical studies

Due to the complexity of OV products and the limited usefulness of animal models, many questions remain to be addressed in early phase clinical studies. This may introduce the need for caution in initial dosing regimens and routes of administration. Since animal dosing information may not provide adequate safety information there is still a need to perform dose ranging studies in cancer trial participants to determine a safe starting dose level. A strategy often used when determining appropriate route of administration has been to follow a stepwise approach starting with intratumoral injection, moving on to regional or local administration, and then to systemic administration. The selected route of administration should be justified and the potential replication of the virus in non-target sites should be considered.

When available, an antiviral therapy against undesired replication of OV or any molecular variants should be considered; e.g., gancyclovir could be useful to control replication of a HSV OV.

4.1 Pharmacokinetics, pharmacodynamics and biological activity

Both PCR and infectivity assays have been used for monitoring levels of OV. Monitoring should be performed in sufficient frequency and duration to detect a possible secondary peak of virus in the blood after administration, suggestive of viral replication in permissive tissues.

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[1] ICH S6 guideline entitled, *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*

Other approaches can be used to monitor the OV including the levels of any encoded viral marker or transgene expression.

Measuring presence and/or distribution of the OV within the tumour can be difficult but useful information can be provided from tumour pathology if resection or biopsy is possible.

4.2 Immunity and immune response

Pre-existing immunity (humoral and/or cellular) to the virus may influence the route of administration, the dosing regimen and the potential value of successive administrations. It is important to monitor for immune responses against the OV product (and, if present, any transgene product).

However, the impact of neutralizing anti-viral antibodies on efficacy is currently not understood. While this immunity is a potential safeguard against excessive viraemia, it might interfere with the goal of virus spread.

Consideration should also be given to the potential impact of inflammatory responses associated with the desired tumour cell lysis.

4.3 Biosafety

It is important that precautions for infectious material and biological safety, and biosafety guidelines or their equivalent, be followed when administering OV. Respective institutional, country, state, and local regulations should be followed. Generally, as part of the clinical protocol, all regulatory authorities require some form of barrier contraception for the duration of the clinical trial as a standard precaution.

Non-clinical viral shedding studies can be useful in preparing for clinical studies and evaluating detection methods. It is advisable to integrate monitoring for shed virus into the clinical development plan.

The consequences of transmission might not be well understood and precautions should be taken to minimize exposure of healthcare providers, family members, and other patient contacts. Extra consideration should be given to minimize the exposure of persons with suppressed or compromised immune systems as well as other relevant populations.

It may be appropriate to instruct the patient and family members in ways to minimise the exposure of others in transit following out-patient administration and in daily life. This may also include the advice to use specific sanitation measures. Many of these considerations might fall under the heading of environmental release/risk and regional authorities should be contacted for details.

２０年度　厚生労働科学研究費補助金　分担研究報告書

包括的な医薬品品質監督システムの国際動向に関する研究

分担研究者　国立医薬品食品衛生研究所薬品部第三室長　檜山　行雄

『医薬品の品質保証の基礎は科学とリスクマネジメントである』との認識から、医薬品規制国際調和会議（ICH）において製剤開発（ICH コード:Q8）および品質リスクマネジメント（ICH コード：Q9）を 2003 年より新トピックとして取り上げた。これらのガイドライン作成が一段落した 2005 年より医薬品品質システム（Q10）の議論が再開された。Q10 の上位概念には、GMP を補完すること、ICH の Q ガイドラインの要点を適用したシステムであること、及び継続的改善を推進するシステムであることの３つが含まれる。昨今起きた原材料流通の問題を踏まえ、外部委託作業及び購入原材料の管理に対し、原則および手順を経営陣の責任の章に盛り込むこととなった。又、ガイドラインの構造を大きく把握してもらうために付属書２には ICHQ10 医薬品品質システムモデルの図解を示し、文章をもって図解を説明することとなった。このような議論を通じ Q10 は最終合意文書であるステップ４に、2008 年 6 月に到達した。日本において Q10 ガイドラインの導入に際し課題となるのが「医薬品、医薬部外品、化粧品及び医療機器の品質管理の基準に関する省令」（GQP 省令）との関係である。従って、Q10 にある原則のひとつ：

「ICH Q10 は、現行の規制要件を越えて新たな期待を創出する意図はない。従って、現行の GMP 要件に付加的な ICH Q10 の内容は任意である。　(ICH Q10 is not intended to create any new expectations beyond current regulatory requirements. Consequently, the content of ICH Q10 that is additional to current regional GMP requirements is optional.)」は「ICH Q10 は、現行の規制要件を越えて新たな期待を創出する意図はない。従って、現行の GMP 要件および医薬品 GQP に付加的な ICH Q10 の内容は任意である。」と読みかえねばならない。

2007 年 11 月横浜非公式会合では、Q8,Q9, Q10 のガイドラインの導入・実践を推進するためには、ICH の作業グループ（IWG）を編成し、事例研究を引用し、Q&A を作成する方針が立てられた。2008 年 6 月の IWG 会議では、Q8, Q9, Q10 に関連する課題をリスト化しおよそ Knowledge management, Quality by Design, Quality system の３つの大きな領域にわける作業を行い、簡単な Q&A は出来るだけ早く公表（2008 年秋か 2009 年春）することが合意された。３つの領域に関する Q&A 案を、日本、アメリカ、欧州の地域を作成担当としてたたき台を作成され、2008 年 11 月の専門家会議で議論され多くの Q&A が仮採択された。仮採択した Q&A 案は各極内で非公式の意見募集を行った。これらの意見には、処方に対するデザインスペース、Process Validation に関する Q&A の要望も含まれた。2009 年 3 月には電話会議が開催され、寄せられた意見も考慮しながら、約 20 の Q&A が最終合意された。

ICH 医薬品品質システムガイドライン（Q10）作成の経過を精査し、Q8、Q9 ガイドラインとともに導入に際しての課題がどのような構図を持つかを考察した。医薬品品質保証のあるべき未来をガイドラインとして示すことが期待される。一方、品質システムを円滑に運営していくために、国際的には他の領域の品質の基準作成を進めることと国内においては基準の統一化が必要と考える。

A　はじめに

18年度の本分担研究（参考文献1）では、医薬品規制国際調和会議（ICH）の品質システム（Q10）ガイドラインにより、『製薬企業に対し、明確な経営者責任、製品ライフサイクルを通じた科学とリスクマネジメントをもって適切な品質保証を求める。一方、"品質システム"を適切に運営すれば、変更手続きの軽減化を含めた継続的改善の機会が与えられる』こととなり、新薬はもとより既存製品に対する規制にも好影響を与えることが期待されると結論した。

19年度の研究（参考文献2）では、ICH Pharmaceutical Quality System (PQS、医薬品品質システム Q10)のステップ2文書にいたる専門家会議の議論および意見聴取の概略を報告した。Q10の上位概念には、GMPを補完すること、ICHのQガイドラインの要点を適用したシステムであること、及び継続的改善を推進するシステムであることの3つが含まれた。2007年夏以降、各極で意見聴取が開始され、日本においては、『経営者の責任』の具現化が困難であること、Q10に先立ち発行された製剤開発（Q8）（参考文献3）及び品質リスクマネジメント（Q9）（参考文献4）ガイドラインとの関連をより明確に示すべきであるとの指摘がされた。2007年の10月のICH非公式会議においては、Q8-Q10を合わせた導入(Implementation)の努力（教育、事例の議論）が必要であることが確認され、Implementation Working Group(IWG)が編成されICH自体が導入作業に関与することが決定された。

20年度はICHQ10の最終合意と日本への導入の課題、並びにQ8-Q10導入に係わる議論の進捗を報告する。

B　医薬品規制国際調和会議（ICH）Pharmaceutical Quality System (医薬品品質システムQ10)の議論の経過

パブリックコメントの概観

個別の記載事項に対する大きな反対意見は見られなかったものの、Q10ガイドラインのみならず、Q8, Q9ガイドラインを合わせた全体像がわかりにくいというコメントが各極ともにあった。又、各項目に対し具体的な解説が欲しいという要望、各極における具体的な導入に関する質問が多く寄せられた。

2008年5月電話会議

2008年6月の専門家会議に向け、パブリックコメントおよびheparinなど最近の原材料流通問題を踏まえ、5月には2度の電話会議が開催され、原材料流通問題に対応するセクションの記述の充実、ガイドライン全体を説明する分かりやすい図の作成の2点を行動方針として採択した。又、ステップ2時点において掲載について、専門家内部（欧州委員会の一部）において異論のあった巻末の「今後見込まれる薬事的アプローチ（Potential Opportunities to Enhance Science and Risk Based Regulatory Approaches を示した表」については、寄せられた意見では、評価が高かったため、最終文書においても収載する方針となった。

2008年6月ポートランド専門家会議

昨今起きた原材料流通の問題は合法内の活動において引き起こされたのではないが、合法内で運営される企業活動のシステム、すなわち品質システムの弱さを反映したものであるとの結論に達した。この結論に基づき、外部委託作業及び購入原材料の管理に対し以下の原則および手順を経営陣の責任の章に盛り込むこととなった。

①医薬品品質システムは、あらゆる外部委託作業及び購入原材料の質の監督及びレビューにまで及ぶ。

②外部委託の運用及び原材料供給者の決定に先立ち、相手方が業務を遂行するまたは規定されたサプライチェーンを用いて原材料を供給する適性及び能力についても審査すること；

(a) 関与する当事者の品質関連活動に対する責任及び情報伝達プロセスを規定すること。外部委託作業については、このことは委託者と受託者間の契約書に含まれること；

(b) 受託者の業務遂行能力または供給者からの原材料の品質をモニタリング及びレビューすること、またあらゆる必要とされる改善を特定及び実施すること；

(c) 入荷した成分及び原材料について、それらが合意されたサプライチェーンを用い、承認された供給源からのものであることを確実とするためにモニタリングを実施すること。

又、ガイドラインの構造を大きく把握してもらうために付属書2には ICHQ10 医薬品品質システムモデルの図解を示し、文章をもって図解を説明することとなった。

このような議論を通じ Q10 は最終合意文書であるステップ4（添付資料1）に到達した。

日本国内の対応

日本においてQ10ガイドラインの導入に際し課題となるのが「医薬品、医薬部外品、化粧品及び医療機器の品質管理の基準に関する省令」（GQP 省令）との関係である。この省令は医薬品工場ごとの GMP では包含されていない、製薬企業（製造販売業者）へ対する品質管理基準であり、以前から認識されていたように、Q10 ガイドラインの少なくない部分と重複がある。

従って、Q10 の 1. 1 にある原則のひとつ：

「ICH Q10 は、現行の規制要件を越えて新たな期待を創出する意図はない。従って、現行の GMP 要件に付加的な ICH Q10 の内容は任意である。(ICH Q10 is not intended to create any new expectations beyond current regulatory requirements. Consequently, the content of ICH Q10 that is additional to current regional GMP requirements is optional.)」は「ICH Q10 は、現行の規制要件を越えて新たな期待を創出する意図はない。従って、現行の GMP 要件および医薬品 GQP に付加的な ICH Q10 の内容は任意である。」と読みかえねばならない。

主なところでは

GQP 省令第 13 条の「自己点検」は Q10 のマネジメントレビューと解釈できる。

マネジメントレビュー

- 上級経営陣は、医薬品品質システムの継続する適切性及び実効性を確実にする、マネジメントレビューを通じ統括管理に責任を有しなければならない。
- 経営陣は、3 章及び 4 章に記載されているように、定期的なプロセス及び製品品質、並びに医薬品品質システムレビューの結果を評価しなければならない。

又、Q10　2．7　「外部委託作業及び購入原材料の管理」における「関与する当事者の品質関連活動に対する責任及び情報伝達プロセスを規定すること。外部委託作業については、このことは委託者と受託者間の契約書に含まれること」という事項は GQP 省令第 7 条の「取り決め」の要件と同義である。

さらに、欧米では枠組みのない製薬企業本社機能（製造販売業者）に対して品質管理関連の査察（GQP 調査）権を日本では行政側が保有している。これらの国内問題は国内内外講演の講演（添付資料2、研究発表 1-9）において言及されている。

以上の導入に際する国内問題を整理した上で Q10 は通知されることが期待される。

C　ICH　Q8, Q9, Q10 Implementation Working Group　(IWG)の進捗

2007 年 11 月横浜非公式会合では、ガイドラインの導入・実践を推進するためには、ICH 外部からの事例研究を引用し、又、ICH の作業グループで Q&A を作成する方針が立てられた。

2008 年 6 月ポートランド 会議

電話会議などを通じ集められていた Q8, Q9, Q10 に関連する課題をリスト化しおよそ Knowledge management, Quality by Design, Quality system の3つの大きな領域にわける作業をまず行った。さらに分科会に分かれ、議論を深めた。この過程において Criticality を単独の課題としては採用しないコンセンサスが形成された。

IWG としての成果物として、簡単な Q&A は出来るだけ早く公表（2008 年秋か 2009 年春）することが合意された。引用する論文・事例などはグローバルに貢献できるものという条件も採択された。2008 年秋のブリュッセル会議までに Knowledge managment, Quality by Design, Quality system の3つの領域に関する Q&A 案を、日本、アメリカ、欧州の地域を作成担当としてたたき台を作成することとなった。この後、電話会議などを通じ、Q&A 案は集計、修正をされ、ブリュッセル専門家会議で調整されることとなった。

2008 年 11 月ブリュッセル専門家会議

合計４２の Q&A 案が集められ、議論され多くが仮採択（添付資料３）された。

Q&A 案の中からリアルタイムリリース (RTR) をとりあげ、説明を試みる RTR とは、端的に言えば、製品品試験結果に代え、工程試験（リアルタイムリリース試験：RTRT）結果を基に出荷判断をすることである。Q&A 案(3.2 Q03、3.2 Q04) では RTRT を設定し上でも最終の製品の規格および試験法の設定は必須あるという原則を示し、RTRT が何らかの理由で RTRT が使えない場合（逸脱）の逸脱管理についても Q&A 案（3.2 Q08, 3.2 Q09）により注意喚起している。

意見募集および 2009 年 3 月電話会議

仮採択した Q&A 案は各極内で非公式の意見募集を行った（添付資料４）。これらの意見には、処方に対するデザインスペース、Process Validation に関する Q&A の要望も含まれた。2009 年 3 月には電話会議が開催され、寄せられた意見も考慮しながら、約 20 の Q&A が最終合意された。20094 月に再度電話会議を開催し、2009 年 6 月開催の横浜専門家会議を含めた IWG の今後の活動計画が調整される。

D 学会などにおける関連する議論

20 年度研究期間内において、ICHQ8-Q10 の導入に関して欧州（発表１）、米国（発表４、添付資料２）、中国（発表 6）で講演の機会に恵まれ、日本国内においても５回を超える発表・講演を行った。

海外における発表では日本の薬事制度の説明にほぼ半分の時間を割き、理解を求めた。欧米間では相互理解が日本に対する理解に比較し、桁違いに進んでいる。承認書という枠組みが現在のところ欧米に存在しないこともあり、Quality by Design に基づいた新薬申請については製造方法の記載を承認申請書にいかにまとめるべきかという課題に多くの質問が寄せられた。

日本の講演では ICHQ8、Q9, Q10 それぞれの関連を強調した。質問は製剤開発、リスクマネジメント、品質システムの中の詳細なものが多く、全体像に関するものは少なかった。発表２では品質関係以外の方々を対象にしたものであった。この講演からは品質関連の業務以外の方々とも共通理解の必要性を痛感した。

2008 年 12 月 ICH ワークショップ北京

APEC 主催による ICH に関するワークショップが中国北京で開催された。

テーマは ICH　Q8 から Q10 のガイドラインの概説およびガイドラインを用いての展望を日米欧の企業、行政代表が講演した（添付資料５）。筆者は日本の薬事法改正の諸規則構築と ICH ガイドラインの関連を述べた。（発表６）中国からの参加者は日本が ICH ガイドライン導入をしつつ製造販売制度(Market Authorization)に移行した点に特に興味を示した。

E 考察

Q10 ガイドライン作成開始時に合意されたスコープ：製品ライフサイクルを通じた包括的品質

システム (Comprehensive quality system for product life cycle)の具体的な上位概念には、

1．現在の GMP を補完するシステム。(complements existing cGMPs or GMPs)
2．ICH の Q ガイドラインの要点を適用したシステム。(focuses on those elements that facilitate application of ICH Quality Guidelines (e.g. ICH(Q8))
3．継続的改善を推進するシステム。(facilitates continuous improvement in pharmaceutical manufacturing)

の 3 つが含まれた。最終合意に達したガイドラインではこれらのスコープは十分満たされているだろうか？原薬プロセス開発のガイドライン(Q11)が完成すれば技術的ガイドラインは網羅されることとなり、Q10 に基づく品質管理監督システムを構築し、運営していくための基礎はできたのではないだろうか。しかし、その一方で、ICH 内外からは Q8、Q9、Q10 を包括的に説明、教育することに対する強い要望があり、それに応えるためには、今後 IWG の活動を通じ、ガイドラインの基本的理解を推進し、協同作業により実践例を増やし共有することが必要である。

「Q10 "品質システム" の下に、官側は企業に明確な経営者責任 (ISO 要素)、製品ライフサイクルを通じた科学 (ICH Q ガイドライン Q1−Q8) とリスクマネジメント (Q9) をもって適切な品質保証を求める。一方、企業側は当該 "品質システム" を適切に運営すれば、変更手続きの軽減化を含めた継続的改善の機会が与えられる」との構図を広げていくためには、深い知識と適切なシステムをもって運営する企業へ対しては手続きなどの軽減化が現実に示されることも必要であろう。

わが国においては新薬に対する基準と既存製品に対する基準は必ずしも同一ではないことが Q10 実践への足かせになる恐れがある。時間をかけてこれらの基準を統一していくことが適切な品質システムの運営上に必要であろうと思われる。

Q8,Q9,Q10 の実践に関して事例研究が世界的に活発に行われている。ここで厚生労働科学研究班により作成された製剤開発申請資料モック（参考文献 5）を参照しながらリアルタイムの品質管理の意義を考察してみる。この事例においては、リアルタイムの品質管理が錠剤の溶出性、含量均一性、含量に対して適用され、最終の品質試験を実行することなく、製造工程内で得られるデータに基づき、出荷の判断が行われるリアルタイムリリースが採用されている。リアルタイムの品質管理を行うためには、製品の規格の項目に対して、どのような（中間製品の）品質特性が寄与しているかの理解と、それらを製造工程中においてリアルタイムに評価できること、さらに、工程条件の調整により品質特性が管理できることが条件となる。リアルタイムの品質管理、つまり工程運転中に連続的に進行を評価し続けることの意義は、品質管理のレベル向上並びに実績データの積み上げによる将来の変更・改善を容易にすることにあると考えられる。Q8 本文にはリアルタイムの品質管理は「出荷試験の（実施）の減少につながる」とされ、用語欄には "「継続（連続）的工程モニター」は工程バリデーションの代替法" と記述されている。又、Q10 の付属書には "Q8,Q9,Q10 の実践を通じプロセスバリデーションの革新的アプローチを可能にする" との記載もある。リアルタイムの品質管理はいままでのバリデーションのパラダイム、つまり「研究開発データに基づき、工程パラメーターを決め、工程が安定していることを仮定し運転をする。」というアプローチを大きく変えていく可能性を秘めているものと考える。

F 結論

ICH 医薬品品質システムガイドライン (Q10) 作成の経過を精査し、Q8、Q9 ガイドラインとともに導入に際しての課題がどのような構図を持つかを考察した。医薬品品質保証のあるべき未来をガイドラインとして示すことが期待される。一方、品質システムを円滑に運営していくために、国際的には他の領域の品質の基準作成を進めることと

国内においては基準の統一化が必要と考える。

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			perspective. However, recently it has become obvious that controlling the quality and consistency of excipients will have a major impact on dosage form development. QbD will drive pharmaceutical companies to have a much better understanding of the functional effect that excipients have on their process than they may have had in the past. As processes have become better controlled, it has become obvious that the variability of excipient properties in formulations can be extremely important to the success of any QbD project. However, due to the fact that many excipients are not made primarily for the pharmaceutical industry, formulators need to build robust formulations which can deal with this variability rather that simply try to tighten specifications that could significantly impact availability of excipients that can be used by Operations. The presentation will review various aspects of excipient variability and why the understanding of how this relates to the development of a QbD design space may be critical to QbD initiatives. It will also discuss the critical need for improved communication between supplier and user concerning excipient process capability and change notification for QbD to be successful.
10:30 am-11:00 am		Break	
11:00 am – 11:30 am	9	Other Risk-Based Efforts in the Global Environment	• Panel Discussion
11:30 am – 12:00 pm		Closing Remarks	• What we have learned and the way forward: Zhang Wei, Director General, Department of Drug Registration, SFDA (China) and Mark Paxton, Associate ViP, International Regulatory Affairs, Pharmaceutical Research and Manufacturers of America (PhRMA) (United States)

ICH Q10 PHARMACEUTICAL QUALITY SYSTEM

ICH Harmonised Tripartite Guideline

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1. PHARMACEUTICAL QUALITY SYSTEM

1.1 Introduction

This document establishes a new ICH tripartite guideline describing a model for an effective *quality* management system for the pharmaceutical industry, referred to as the *Pharmaceutical Quality System*. Throughout this guideline, the term "pharmaceutical quality system" refers to the ICH Q10 model.

ICH Q10 describes one comprehensive model for an effective pharmaceutical quality system that is based on International Standards Organisation (ISO) quality concepts, includes applicable Good Manufacturing Practice (GMP) regulations and complements ICH Q8 "Pharmaceutical Development" and ICH Q9 "Quality Risk Management". ICH Q10 is a model for a pharmaceutical quality system that can be implemented throughout the different stages of a product lifecycle. Much of the content of ICH Q10 applicable to manufacturing sites is currently specified by regional GMP requirements. ICH Q10 is not intended to create any new expectations beyond current regulatory requirements. Consequently, the content of ICH Q10 that is additional to current regional GMP requirements is optional.

ICH Q10 demonstrates industry and regulatory authorities' support of an effective pharmaceutical quality system to enhance the quality and availability of medicines around the world in the interest of public health. Implementation of ICH Q10 throughout the product lifecycle should facilitate *innovation* and *continual improvement* and strengthen the link between pharmaceutical development and manufacturing activities.

1.2 Scope

This guideline applies to the systems supporting the development and manufacture of pharmaceutical drug substances (i.e., API) and drug products, including biotechnology and biological products, throughout the product lifecycle.

The elements of ICH Q10 should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognising the differences among, and the different goals of each stage (see Section 3).

For the purposes of this guideline, the product lifecycle includes the following technical activities for new and existing products:

- Pharmaceutical Development
  - Drug substance development;
  - Formulation development (including container/closure system);
  - Manufacture of investigational products;
  - Delivery system development (where relevant);
  - Manufacturing process development and scale-up;
  - Analytical method development.

- Technology Transfer
  - New product transfers during Development through Manufacturing;
  - Transfers within or between manufacturing and testing sites for marketed products.

- Commercial Manufacturing
  - Acquisition and control of materials;
  - Provision of facilities, utilities, and equipment;
  - Production (including packaging and labelling);
  - Quality control and assurance;
  - Release;
  - Storage;
  - Distribution (excluding wholesaler activities).

- Product Discontinuation
  - Retention of documentation;
  - Sample retention;
  - Continued product assessment and reporting.

1.3 Relationship of ICH Q10 to Regional GMP Requirements, ISO Standards and ICH Q7

Regional GMP requirements, the ICH Q7 Guideline, "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients", and ISO quality management system guidelines form the foundation for ICH Q10. To meet the objectives described below, ICH Q10 augments GMPs by describing specific quality system elements and management responsibilities. ICH Q10 provides a harmonised model for a pharmaceutical quality system throughout the lifecycle of a product and is intended to be used together with regional GMP requirements.

The regional GMPs do not explicitly address all stages of the product lifecycle (e.g., Development). The quality system elements and management responsibilities described in this guideline are intended to encourage the use of science and risk based approaches at each lifecycle stage, thereby promoting continual improvement across the entire product lifecycle.

1.4 Relationship of ICH Q10 to Regulatory Approaches

Regulatory approaches for a specific product or manufacturing facility should be commensurate with the level of product and process understanding, the results of *quality risk management*, and the effectiveness of the pharmaceutical quality system. When implemented, the effectiveness of the pharmaceutical quality system can normally be evaluated during a regulatory inspection at the manufacturing site. Potential opportunities to enhance science and risk based regulatory approaches are identified in Annex 1. Regulatory processes will be determined by region.

1.5 ICH Q10 Objectives

Implementation of the Q10 model should result in achievement of three main objectives which complement or enhance regional GMP requirements.

1.5.1 Achieve *Product Realisation*

To establish, implement and maintain a system that allows the delivery of products with the

quality attributes appropriate to meet the needs of patients, health care professionals, regulatory authorities (including compliance with approved regulatory filings) and other internal and external customers.

1.5.2 Establish and Maintain a *State of Control*

To develop and use effective monitoring and control systems for process performance and product quality, thereby providing assurance of continued suitability and *capability of processes*. Quality risk management can be useful in identifying the monitoring and control systems.

1.5.3 Facilitate Continual Improvement

To identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations and pharmaceutical quality system enhancements, thereby increasing the ability to fulfil quality needs consistently. Quality risk management can be useful for identifying and prioritising areas for continual improvement.

1.6 *Enablers*: Knowledge Management and Quality Risk Management

Use of *knowledge management* and quality risk management will enable a company to implement ICH Q10 effectively and successfully. These enablers will facilitate achievement of the objectives described in Section 1.5 above by providing the means for science and risk based decisions related to product quality.

1.6.1 Knowledge Management

Product and process knowledge should be managed from development through the commercial life of the product up to and including product discontinuation. For example, development activities using scientific approaches provide knowledge for product and process understanding. Knowledge management is a systematic approach to acquiring, analysing, storing and disseminating information related to products, manufacturing processes and components. Sources of knowledge include, but are not limited to prior knowledge (public domain or internally documented); pharmaceutical development studies; technology transfer activities; process validation studies over the product lifecycle; manufacturing experience; innovation; continual improvement; and *change management* activities.

1.6.2 Quality risk Management

Quality risk management is integral to an effective pharmaceutical quality system. It can provide a proactive approach to identifying, scientifically evaluating and controlling potential risks to quality. It facilitates continual improvement of process performance and product quality throughout the product lifecycle. ICH Q9 provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality.

1.7 Design and Content Considerations

(a) The design, organisation and documentation of the pharmaceutical quality system should be well structured and clear to facilitate common understanding and consistent application.

(b) The elements of ICH Q10 should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognising the different goals and knowledge available for each stage.

(c) The size and complexity of the company's activities should be taken into consideration when developing a new pharmaceutical quality system or modifying an existing one. The design of the pharmaceutical quality system should incorporate appropriate risk management principles. While some aspects of the pharmaceutical quality system can be company-wide and others site-specific, the effectiveness of the pharmaceutical quality system is normally demonstrated at the site level.

(d) The pharmaceutical quality system should include appropriate processes, resources and responsibilities to provide assurance of the quality of *outsourced activities* and purchased materials as described in Section 2.7.

(e) Management responsibilities, as described in Section 2, should be identified within the pharmaceutical quality system.

(f) The pharmaceutical quality system should include the following elements, as described in Section 3: process performance and product quality monitoring, *corrective* and *preventive action*, change management and management review.

(g) *Performance indicators*, as described in Section 4, should be identified and used to monitor the effectiveness of processes within the pharmaceutical quality system.

1.8 Quality Manual

A *Quality Manual* or equivalent documentation approach should be established and should contain the description of the pharmaceutical quality system. The description should include:

(a) The *quality policy* (see Section 2);

(b) The scope of the pharmaceutical quality system;

(c) Identification of the pharmaceutical quality system processes, as well as their sequences, linkages and interdependencies. Process maps and flow charts can be useful tools to facilitate depicting pharmaceutical quality system processes in a visual manner;

(d) Management responsibilities within the pharmaceutical quality system (see Section 2).

2. MANAGEMENT RESPONSIBILITY

Leadership is essential to establish and maintain a company-wide commitment to quality and for the performance of the pharmaceutical quality system.

2.1 Management Commitment

(a) *Senior management* has the ultimate responsibility to ensure an effective pharmaceutical quality system is in place to achieve the *quality objectives*, and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the company.

(b) Management should:

(1) Participate in the design, implementation, monitoring and maintenance of an effective pharmaceutical quality system;
(2) Demonstrate strong and visible support for the pharmaceutical quality system and ensure its implementation throughout their organisation;
(3) Ensure a timely and effective communication and escalation process exists to raise quality issues to the appropriate levels of management;
(4) Define individual and collective roles, responsibilities, authorities and inter-relationships of all organisational units related to the pharmaceutical quality system. Ensure these interactions are communicated and understood at all levels of the organisation. An independent quality unit/structure with authority to fulfil certain pharmaceutical quality system responsibilities is required by regional regulations;
(5) Conduct management reviews of process performance and product quality and of the pharmaceutical quality system;
(6) Advocate continual improvement;
(7) Commit appropriate resources.

2.2 Quality Policy

(a) Senior management should establish a quality policy that describes the overall intentions and direction of the company related to quality.

(b) The quality policy should include an expectation to comply with applicable regulatory requirements and should facilitate continual improvement of the pharmaceutical quality system.

(c) The quality policy should be communicated to and understood by personnel at all levels in the company.

(d) The quality policy should be reviewed periodically for continuing effectiveness.

2.3 *Quality Planning*

(a) Senior management should ensure the quality objectives needed to implement the quality policy are defined and communicated.

(b) Quality objectives should be supported by all relevant levels of the company.

(c) Quality objectives should align with the company's strategies and be consistent with the quality policy.

(d) Management should provide the appropriate resources and training to achieve the quality objectives.

(e) Performance indicators that measure progress against quality objectives should be established, monitored, communicated regularly and acted upon as appropriate as described in Section 4.1 of this document.

2.4 Resource Management

(a) Management should determine and provide adequate and appropriate resources (human, financial, materials, facilities and equipment) to implement and maintain the

pharmaceutical quality system and continually improve its effectiveness.

(b) Management should ensure that resources are appropriately applied to a specific product, process or site.

2.5 Internal Communication

(a) Management should ensure appropriate communication processes are established and implemented within the organisation.

(b) Communications processes should ensure the flow of appropriate information between all levels of the company.

(c) Communication processes should ensure the appropriate and timely escalation of certain product quality and pharmaceutical quality system issues.

2.6 Management Review

(a) Senior management should be responsible for pharmaceutical quality system governance through management review to ensure its continuing suitability and effectiveness.

(b) Management should assess the conclusions of periodic reviews of process performance and product quality and of the pharmaceutical quality system, as described in Sections 3 and 4.

2.7 Management of Outsourced Activities and Purchased Materials

The pharmaceutical quality system, including the management responsibilities described in this section, extends to the control and review of any outsourced activities and quality of purchased materials. The pharmaceutical company is ultimately responsible to ensure processes are in place to assure the control of outsourced activities and quality of purchased materials. These processes should incorporate quality risk management and include:

(a) Assessing prior to outsourcing operations or selecting material suppliers, the suitability and competence of the other party to carry out the activity or provide the material using a defined supply chain (e.g., audits, material evaluations, qualification);

(b) Defining the responsibilities and communication processes for quality-related activities of the involved parties. For outsourced activities, this should be included in a written agreement between the contract giver and contract acceptor;

(c) Monitoring and review of the performance of the contract acceptor or the quality of the material from the provider, and the identification and implementation of any needed improvements;

(d) Monitoring incoming ingredients and materials to ensure they are from approved sources using the agreed supply chain.

2.8 Management of Change in Product Ownership

When product ownership changes, (e.g., through acquisitions) management should consider the complexity of this and ensure:

(a) The ongoing responsibilities are defined for each company involved;

(b) The necessary information is transferred.

3. CONTINUAL IMPROVEMENT OF PROCESS PERFORMANCE AND PRODUCT QUALITY

This section describes the lifecycle stage goals and the four specific pharmaceutical quality system elements that augment regional requirements to achieve the ICH Q10 objectives, as defined in Section 1.5. It does not restate all regional GMP requirements.

3.1 Lifecycle Stage Goals

The goals of each product lifecycle stage are described below.

3.1.1 Pharmaceutical Development

The goal of pharmaceutical development activities is to design a product and its manufacturing process to consistently deliver the intended performance and meet the needs of patients and healthcare professionals, and regulatory authorities and internal customers' requirements. Approaches to pharmaceutical development are described in ICH Q8. The results of exploratory and clinical development studies, while outside the scope of this guidance, are inputs to pharmaceutical development.

3.1.2 Technology Transfer

The goal of technology transfer activities is to transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realisation. This knowledge forms the basis for the manufacturing process, *control strategy*, process validation approach and ongoing continual improvement.

3.1.3 Commercial Manufacturing

The goals of manufacturing activities include achieving product realisation, establishing and maintaining a state of control and facilitating continual improvement. The pharmaceutical quality system should assure that the desired product quality is routinely met, suitable process performance is achieved, the set of controls are appropriate, improvement opportunities are identified and evaluated, and the body of knowledge is continually expanded.

3.1.4 Product Discontinuation

The goal of product discontinuation activities is to manage the terminal stage of the product lifecycle effectively. For product discontinuation, a pre-defined approach should be used to manage activities such as retention of documentation and samples and continued product assessment (e.g., complaint handling and stability) and reporting in accordance with regulatory requirements.

3.2 Pharmaceutical Quality System Elements

The elements described below might be, required in part under regional GMP regulations. However, the Q10 model's intent is to enhance these elements in order to promote the lifecycle approach to product quality. These four elements are:

- Process performance and product quality monitoring system;
- *Corrective action* and *preventive action* (CAPA) system;
- Change management system;
- Management review of process performance and product quality.

These elements should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognising the differences among, and the different goals of, each stage. Throughout the product lifecycle, companies are encouraged to evaluate opportunities for innovative approaches to improve product quality.

Each element is followed by a table of example applications of the element to the stages of the pharmaceutical lifecycle.

3.2.1 Process Performance and Product Quality Monitoring System

Pharmaceutical companies should plan and execute a system for the monitoring of process performance and product quality to ensure a state of control is maintained. An effective monitoring system provides assurance of the continued capability of processes and controls to produce a product of desired quality and to identify areas for continual improvement. The process performance and product quality monitoring system should:

(a) Use quality risk management to establish the control strategy. This can include parameters and attributes related to drug substance 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. The control strategy should facilitate timely *feedback / feedforward* and appropriate corrective action and preventive action;

(b) Provide the tools for measurement and analysis of parameters and attributes identified in the control strategy (e.g., data management and statistical tools);

(c) Analyse parameters and attributes identified in the control strategy to verify continued operation within a state of control;

(d) Identify sources of variation affecting process performance and product quality for potential continual improvement activities to reduce or control variation;

(e) Include feedback on product quality from both internal and external sources, e.g., complaints, product rejections, non-conformances, recalls, deviations, audits and regulatory inspections and findings;

(f) Provide knowledge to enhance process understanding, enrich the *design space* (where established), and enable innovative approaches to process validation.

Table I: Application of Process Performance and Product Quality Monitoring System throughout the Product Lifecycle

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Process and product knowledge generated and process and product monitoring conducted throughout development can be used to establish a control strategy for manufacturing.	Monitoring during scale-up activities can provide a preliminary indication of process performance and the successful integration into manufacturing. Knowledge obtained during transfer and scale up activities can be useful in further developing the control strategy.	A well-defined system for process performance and product quality monitoring should be applied to assure performance within a state of control and to identify improvement areas.	Once manufacturing ceases, monitoring such as stability testing should continue to completion of the studies. Appropriate action on marketed product should continue to be executed according to regional regulations.

3.2.2 Corrective Action and Preventive Action (CAPA) System

The pharmaceutical company should have a system for implementing corrective actions and preventive actions resulting from the investigation of complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance and product quality monitoring. A structured approach to the investigation process should be used with the objective of determining the root cause. The level of effort, formality, and documentation of the investigation should be commensurate with the level of risk, in line with ICH Q9. CAPA methodology should result in product and process improvements and enhanced product and process understanding.

Table II: Application of Corrective Action and Preventive Action System throughout the Product Lifecycle

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Product or process variability is explored. CAPA methodology is useful where corrective actions and preventive actions are incorporated into the iterative design and development process.	CAPA can be used as an effective system for feedback, feedforward and continual improvement.	CAPA should be used and the effectiveness of the actions should be evaluated.	CAPA should continue after the product is discontinued. The impact on product remaining on the market should be considered as well as other products which might be impacted.

3.2.3 Change Management System

Innovation, continual improvement, the outputs of process performance and product quality monitoring and CAPA drive change. In order to evaluate, approve and implement these changes properly, a company should have an effective change management system. There is generally a difference in formality of change management processes prior to the initial regulatory submission and after submission, where changes to the regulatory filing might be required under regional requirements.

The change management system ensures continual improvement is undertaken in a timely and effective manner. It should provide a high degree of assurance there are no unintended consequences of the change.

The change management system should include the following, as appropriate for the stage of the lifecycle:

(a) Quality risk management should be utilised to evaluate proposed changes. The level of effort and formality of the evaluation should be commensurate with the level of risk;

(b) Proposed changes should be evaluated relative to the marketing authorisation, including design space, where established, and/or current product and process understanding. There should be an assessment to determine whether a change to the regulatory filing is required under regional requirements. As stated in ICH Q8, working within the design space is not considered a change (from a regulatory filing perspective). However, from a pharmaceutical quality system standpoint, all changes should be evaluated by a company's change management system;

(c) Proposed changes should be evaluated by expert teams contributing the appropriate expertise and knowledge from relevant areas (e.g., Pharmaceutical Development, Manufacturing, Quality, Regulatory Affairs and Medical), to ensure the change is technically justified. Prospective evaluation criteria for a proposed change should be set;

(d) After implementation, an evaluation of the change should be undertaken to confirm the change objectives were achieved and that there was no deleterious impact on product quality.

Table III: Application of Change Management System throughout the Product Lifecycle

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Change is an inherent part of the development process and should be documented; the formality of the change management process should be consistent with the stage of pharmaceutical development.	The change management system should provide management and documentation of adjustments made to the process during technology transfer activities.	A formal change management system should be in place for commercial manufacturing. Oversight by the quality unit should provide assurance of appropriate science and risk based assessments.	Any changes after product discontinuation should go through an appropriate change management system.