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平成26年度分担研究報告書

－遺伝毒性不純物に関する研究－

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研究要旨

医薬品中には、合成過程の試薬や反応中間体、副産物、もしくは分解物等が不純物として存在することがあり、これら不純物の安全にも注意を向ける必要がある。特にそれら不純物に遺伝毒性が疑われた場合は、たとえその不純物が微量であったとしても、適切なリスク評価と管理が必要である。医薬品中の遺伝毒性不純物に関する国際的ガイドライン（ICH-M7）策定のための専門家会議（EWG）は2010年11月の福岡会議から開始され、2012年11月のサンティエゴ会議においてStep2に至った。本年度は、Step2のドラフトガイドラインにパブリックコメントを反映させ、2014年６月のミネアポリス会議で最終化に至った（Step4）。最終化にあたり、M7ガイドラインは、現在開発中の医薬品に関しては、18ヶ月は適用されないなどの猶予期間を設けることが合意された。

キーワード：ICHガイドライン、遺伝毒性不純物、変異原性、リスク管理

A．研究目的

医薬品中には、合成過程の試薬や反応中間体、副産物、もしくは分解物等が不純物として存在することがあり、これら不純物の安全にも注意を向ける必要がある。ICHのQ3ガイドラインでは医薬品（原薬および製剤）の不純物の規格限度値に関して、最大一日投与量に基づく安全性確認の閾値を規定し、それを超えるものについては、安全性を確認するための試験を求めている。しかしながら、それら不純物に遺伝毒性が疑われた場合はやっかいである。一般に遺伝毒性物質には閾値がないとされているため、たとえその不純物が微量であったとしても、その暴露による突然変異や染色体異常等の影響は否定できない。従って、ICH-Q3ガイドラインでの不純物の規格限度値は遺伝毒性不純物には適応できない。また、このガイドラインは治験薬には適応されないため、臨床試験でのボランティアや、治験患者の安全性確認は考慮されていない。

2006年、欧州医薬品庁（EMEA）は医薬品の遺伝毒性不純物に関するガイドラインを発表し、また米国FDAも2008年に同様のドラフトガイダンスを提出した。これを受けて2010年から日本、欧州、米国による国際ガイドライン（ICH-M7）の策定が開始された。本年度は、一昨年にStep2となった本ガイドライ

ンにパブリックコメントを反映させ、2014年６月のミネアポリス会議で最終化することができた。

B．研究方法

平成26年度の研究は規制側として国立衛研の本間、阿曽、PMDAの柊、福地が、企業側からはJPMAの橋爪、小松、福津、井越がICH-M7の専門家会議（EWG）に参画するとともに、国内での調査研究を行い、ガイドラインの策定に携わった。

C．研究結果

2014年６月２～５日のミネアポリス会議でM7ガイドラインが最終化され（Step4）、３局によるサインオフがなされた。その後、６月23日にICHホームページにStep4文書が公開された（資料１）。

以下、最終化に至ったミネアポリス会議での論点を概説する。

Ⅰ．安全性に関する論点

① ハザード評価

不純物、存在する可能性のある不純物をクラス分類し、不純物の許容摂取量を決める。データベースおよび文献検索により、不純物のがん原性およびAmes変異原性データを検索し、クラス分類する。

変異原性が不明なクラス３の不純物に関しては、異なる２種類の（Q）SARシステム（知識ベース、統計ベース）を用い、変異原性を予測する。２種類の（Q）SAR評価の結果によりアラート構造が示されない限りは、変異原性の懸念がないと結論可能である。異なる予測結果が得られた場合は、専門的な知識によりレビューすることができる。また、陽性結果がでてもAmes試験を実施し陰性であればクラス５（変異原性なし）とする。（Q）SARを実施せずAmes試験を実施することも可能である。

② リスクの特性解析

● TTCに基づく許容摂取量

変異原性不純物のTTCに基づく許容摂取量である1.5 μg/人/dayは、リスクが無視できる程度（理論上の過剰発がんリスクは生涯曝露において10万分の１未満）とみなされており、一般的には多くの医薬品不純物に対し、管理に用いる許容限度値を算出する既定値として使用できる。この方法は通常、長期投与（10年超）を目的とした医薬品中の発がん性データが得られていない変異原性不純物に使用される（クラス２及び３）。

● 化合物特異的な許容摂取量

十分な発がん性データが存在する場合、許容摂取量の算出を目的とした化合物特異的なリスク評価を、TTCに基づく許容摂取量の代わりに適用するべきである。既知の変異原性発がん物質については、発がん性の強さを直線外挿する既定の方法により、化合物特異的許容摂取量を算出できる。あるいは、国際的規制機関で使用されているような確立された他のリスク評価手法を適用して許容摂取量を算出したり、規制当局が公表している既存値を使用したりしてもよい。また、EWGでは医薬品不純物として頻発する不純物を、Addendumとして個別許容摂取量を例示する予定である。

● 一生涯よりも短い期間（LTL）の曝露に関する許容摂取量

既知の発がん物質の標準的リスク評価では、累積投与量に応じて発がんリスクが増加すると想定している。したがって、一生涯にわたって連続的に低用量で投与される場合の発がんリスクは、同一の累積曝露量をより短期間に平均して投与した場合と同等と考えられる。このようなLTLに基づく許容摂取量はこれまでと同じであるが、市販製品に対しては、投与期間と許容摂取量の分類は、大部分の患者が曝露されると予期される期間に対して適用することを意図している。これらの摂取量を適用するにあたって、様々なシナリオにともなった摂取量の案を新たに表に記載した。

③ Q3A/Bガイドラインとの整合性

ICH M7ガイドラインの勧告では、不純物が遺伝子突然変異を引き起こす可能性を評価するための最新の手法が示され、そのような不純物が安全なレベルに管理できることを確実にしているため、安全性確認の必要な閾値よりも低いか高いかを問わず、変異原性に関するさらなる安全性評価を行う必要はない。長期投与において１日あたりの不純物の量が１mgを超える場合は、ICH Q3A/Q3Bに従い、遺伝毒性評

価を考慮する。1 mg以下である場合は、その必要はない。

④ ガイドラインの実施（猶予期間）

M7は公開後に実施が推奨される。ただし、ガイドラインが複雑であるため、ICHでの公開18ヵ月後までは、M7の適用は求められない。商業生産工程の開発も同様の課題が伴うことを考慮し、M7がICHで公開されてから36ヵ月後までは、第Ⅱb相又は第Ⅲ相治験を含まない新規製造販売承認申請へのM7の適用は求められないものとする。

Ⅱ．品質に関する論点

① 市販製品に関するその他の検討事項

懸念される特別な理由があれば、市販製品への本ガイドラインの適用が必要となる場合がある。「cohort of concern」に分類される構造でない限り、不純物に警告構造が認められるだけでは追加措置を開始するのに不十分と考えられる。しかしながら、製造販売承認申請のための全般的な管理戦略及び規格を確立した後に得られた不純物に関連する新たなハザードデータ（クラス１又は２に分類）は、懸念される特別な理由と考えられる。この不純物に関連する新たなハザードデータは、関連する規制上の試験ガイドラインに適合する質の高い科学研究によって得られたものとし、データ記録又は報告書が容易に入手できる必要がある。同様に、既知のクラス１又はクラス２の変異原性物質が市販製品中に新たに確認された場合についても、懸念の理由となり得る。これらいずれの場合においても、申請者がこの新たな情報を知ったときには、本ガイドラインに従い評価を行うべきである。

② 製造工程と製剤中の不純物に関する評価

構造を決定した不純物のうち、出発物質及び中間体中に認められている不純物、並びに出発物質から原薬に至る合成ルートにおいて合理的に予想される副生成物については、原薬に持ち越されるリスクを評価すべきである。一部の不純物については、原薬に持ち越されるリスクはほとんどないと考えられるため（例えば、長い合成ルートの初期合成段階における不純物など）、ある工程以降から不純物の変異原性を評価することに関し、その妥当性をリスクに基づいて示すことができる。

③ 製造工程由来不純物の管理

原料、出発物質又は中間体の規格に不純物の試験を含めるか、工程内管理として不純物の試験を実施し、適切な分析法を用いて原薬中の不純物の許容限度値を超える値を判定基準とする。加えて、実証された不純物の挙動と除去及び関連する工程管理により、後続する工程において追加試験を必要とせずとも、原薬中の不純物レベルが許容限度値未満であることを保証する。

工程パラメータと残留する不純物のレベルに与える影響（不純物の挙動と除去に関する知識を含む）について十分な確信をもって理解されており、この不純物に対する試験が必要とされないほど原薬の不純物のレベルが許容限度値未満となる（すなわち、いずれの規格にも不純物を記載する必要がない）。

④ 分解物の管理

湿度、光又は酸素から保護するために設計された製剤開発や包装により分解を低減する。製剤開発や包装設計によっても変異原性分解生成物のレベルを許容限度値未満に管理できないことが予測され、そのレベルが合理的に実行可能な限り低減したものである場合、リスク・ベネフィット分析に基づき、より高い許容限度値を正当化できる。

⑤ 治験届時の品質に関する資料

本邦では治験薬の品質に関する資料の提出は生物医薬品以外の治験薬については求めておらず、化学合成の医薬品について、治験届時に品質に関する資料については今後の議論が必要である。

D．考　察

2010年から策定が開始されたICH-M7ガイドラインは、2014年６月のミネアポリス会議で無事最終化することができた。現在、国内実施に向けたStep5文書の作成、医薬品不純物として頻発する不純物の許容摂取量に関するAddendumの作成作業が進行中である。本Addendumは2015年３月にStep2、2015年中に最終化の予定である。

E．結　論

医薬品中には、合成過程の試薬や反応中間体、副産物、もしくは分解物等が不純物として存在することがあり、これら不純物の安全にも注意を向ける必要がある。特にそれら不純物に遺伝毒性が疑われた場合は、たとえその不純物が微量であったとしても、適切なリスク評価と管理が必要である。医薬品中の遺伝毒性不純物に関する国際的ガイドライン（ICH-M7）策定のための専門家会議（EWG）は2010年11月の福岡会議から開始され、2014年６月のミネアポリス会議で無事最終化することができた。本ガイドラインには臨床開発中および承認後の医薬品に含まれる変異原性不純物のリスク評価と管理のための様々な手法が取り入れられている。

F．健康危機情報

特になし

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Ｈ．知的所有権の取得状況

なし

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

ASSESSMENT AND CONTROL OF DNA REACTIVE (MUTAGENIC) IMPURITIES IN PHARMACEUTICALS TO LIMIT POTENTIAL CARCINOGENIC RISK

M7

Current *Step 4* version

dated 23 June 2014

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

M7
Document History

Code	History	Date
M7	Approval by the Steering Committee under *Step 2* and release for public consultation.	6 February 2013
M7	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	5 June 2014

Current *Step 4* version

M7	Corrigendum to fix typographical errors and replace word "degradants" with "degradation products" throughout the document.	23 June 2014

Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 5 June 2014, this Guideline is recommended for adoption to the three regulatory parties to ICH

TABLE OF CONTENTS

ASSESSMENT AND CONTROL OF DNA REACTIVE (MUTAGENIC) IMPURITIES IN PHARMACEUTICALS TO LIMIT POTENTIAL CARCINOGENIC RISK

1. INTRODUCTION

The synthesis of drug substances involves the use of reactive chemicals, reagents, solvents, catalysts, and other processing aids. As a result of chemical synthesis or subsequent degradation, impurities reside in all drug substances and associated drug products. While ICH Q3A(R2): Impurities in New Drug Substances and Q3B(R2): Impurities in New Drug Products (Ref. 1, 2) provides guidance for qualification and control for the majority of the impurities, limited guidance is provided for those impurities that are DNA reactive. The purpose of this guideline is to provide a practical framework that is applicable to the identification, categorization, qualification, and control of these mutagenic impurities to limit potential carcinogenic risk. This guideline is intended to complement ICH Q3A(R2), Q3B(R2) (Note 1), and ICH M3(R2): Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorizations for Pharmaceuticals (Ref. 3).

This guideline emphasizes considerations of both safety and quality risk management in establishing levels of mutagenic impurities that are expected to pose negligible carcinogenic risk. It outlines recommendations for assessment and control of mutagenic impurities that reside or are reasonably expected to reside in final drug substance or product, taking into consideration the intended conditions of human use.

2. SCOPE OF GUIDELINE

This document is intended to provide guidance for new drug substances and new drug products during their clinical development and subsequent applications for marketing. It also applies to post-approval submissions of marketed products, and to new marketing applications for products with a drug substance that is present in a previously approved product, in both cases only where:

- Changes to the drug substance synthesis result in new impurities or increased acceptance criteria for existing impurities;
- Changes in the formulation, composition or manufacturing process result in new degradation products or increased acceptance criteria for existing degradation products;
- Changes in indication or dosing regimen are made which significantly affect the acceptable cancer risk level.

Assessment of the mutagenic potential of impurities as described in this guideline is not intended for the following types of drug substances and drug products: biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation products, herbal products, and crude products of animal or plant origin.

This guideline does not apply to drug substances and drug products intended for advanced cancer indications as defined in the scope of ICH S9 (Ref. 4). Additionally, there may be some cases where a drug substance intended for other indications is itself genotoxic at therapeutic concentrations and may be expected to be associated with an increased cancer risk. Exposure to a mutagenic impurity in these cases would not

significantly add to the cancer risk of the drug substance. Therefore, impurities could be controlled at acceptable levels for non-mutagenic impurities.

Assessment of the mutagenic potential of impurities as described in this guideline is not intended for excipients used in existing marketed products, flavoring agents, colorants, and perfumes. Application of this guideline to leachables associated with drug product packaging is not intended, but the safety risk assessment principles outlined in this guideline for limiting potential carcinogenic risk can be used if warranted. The safety risk assessment principles of this guideline can be used if warranted for impurities in excipients that are used for the first time in a drug product and are chemically synthesized.

3. GENERAL PRINCIPLES

The focus of this guideline is on DNA reactive substances that have a potential to directly cause DNA damage when present at low levels leading to mutations and therefore, potentially causing cancer. This type of mutagenic carcinogen is usually detected in a bacterial reverse mutation (mutagenicity) assay. Other types of genotoxicants that are non-mutagenic typically have threshold mechanisms and usually do not pose carcinogenic risk in humans at the level ordinarily present as impurities. Therefore to limit a possible human cancer risk associated with the exposure to potentially mutagenic impurities, the bacterial mutagenicity assay is used to assess the mutagenic potential and the need for controls. Structure-based assessments are useful for predicting bacterial mutagenicity outcomes based upon the established knowledge. There are a variety of approaches to conduct this evaluation including a review of the available literature, and/or computational toxicology assessment.

A Threshold of Toxicological Concern (TTC) concept was developed to define an acceptable intake for any unstudied chemical that poses a negligible risk of carcinogenicity or other toxic effects. The methods upon which the TTC is based are generally considered to be very conservative since they involve a simple linear extrapolation from the dose giving a 50% tumor incidence (TD_{50}) to a 1 in 10^6 incidence, using TD_{50} data for the most sensitive species and most sensitive site of tumor induction. For application of a TTC in the assessment of acceptable limits of mutagenic impurities in drug substances and drug products, a value of 1.5 μg/day corresponding to a theoretical 10^{-5} excess lifetime risk of cancer, can be justified. Some structural groups were identified to be of such high potency that intakes even below the TTC would theoretically be associated with a potential for a significant carcinogenic risk. This group of high potency mutagenic carcinogens referred to as the "cohort of concern", comprises aflatoxin-like-, N-nitroso-, and alkyl-azoxy compounds.

During clinical development, it is expected that control strategies and approaches will be less developed in earlier phases where overall development experience is limited. This guideline bases acceptable intakes for mutagenic impurities on established risk assessment strategies. Acceptable risk during the early development phase is set at a theoretically calculated level of approximately one additional cancer per million. For later stages in development and for marketed products, acceptable increased cancer risk is set at a theoretically calculated level of approximately one in one hundred thousand. These risk levels represent a small theoretical increase in risk when compared to human overall lifetime incidence of developing any type of cancer, which is greater than 1 in 3. It is noted that established cancer risk assessments are based on lifetime exposures. Less-Than-Lifetime (LTL) exposures both during development and marketing can have higher acceptable intakes of impurities and still maintain comparable risk levels. The use of a numerical cancer risk value (1 in 100,000) and its translation into risk-based

doses (TTC) is a highly hypothetical concept that should not be regarded as a realistic indication of the actual risk. Nevertheless, the TTC concept provides an estimate of safe exposures for any mutagenic compound. However, exceeding the TTC is not necessarily associated with an increased cancer risk given the conservative assumptions employed in the derivation of the TTC value. The most likely increase in cancer incidence is actually much less than 1 in 100,000. In addition, in cases where a mutagenic compound is a non-carcinogen in a rodent bioassay, there would be no predicted increase in cancer risk. Based on all the above considerations, any exposure to an impurity that is later identified as a mutagen is not necessarily associated with an increased cancer risk for patients already exposed to the impurity. A risk assessment would determine whether any further actions would be taken.

Where a potential risk has been identified for an impurity, an appropriate control strategy leveraging process understanding and/or analytical controls should be developed to ensure that the mutagenic impurity is at or below the acceptable cancer risk level.

There may be cases when an impurity is also a metabolite of the drug substance. In such cases the risk assessment that addresses mutagenicity of the metabolite can qualify the impurity.

4. CONSIDERATIONS FOR MARKETED PRODUCTS

This guideline is not intended to be applied retrospectively (i.e., to products marketed prior to adoption of this guideline). However, some types of post-approval changes warrant a reassessment of safety relative to mutagenic impurities. This section applies to these post-approval changes for products marketed prior to, or after, the adoption of this guideline. Section 8.5 (Lifecycle Management) contains additional recommendations for products marketed after adoption of this guideline.

4.1 Post-Approval Changes to the Drug Substance Chemistry, Manufacturing, and Controls

Post-approval submissions involving the drug substance chemistry, manufacturing, and controls should include an evaluation of the potential risk impact associated with mutagenic impurities from changes to the route of synthesis, reagents, solvents, or process conditions after the starting material. Specifically, changes should be evaluated to determine if the changes result in any new mutagenic impurities or higher acceptance criteria for existing mutagenic impurities. Reevaluation of impurities not impacted by changes is not recommended. For example, when only a portion of the manufacturing process is changed, the assessment of risk from mutagenic impurities should be limited to whether any new mutagenic impurities result from the change, whether any mutagenic impurities formed during the affected step are increased, and whether any known mutagenic impurities from up-stream steps are increased. Regulatory submissions associated with such changes should describe the assessment as outlined in Section 9.2. Changing the site of manufacture of drug substance, intermediates, or starting materials or changing raw materials supplier will not require a reassessment of mutagenic impurity risk.

When a new drug substance supplier is proposed, evidence that the drug substance produced by this supplier using the same route of synthesis as an existing drug product marketed in the assessor's region is considered to be sufficient evidence of acceptable risk/benefit regarding mutagenic impurities and an assessment per this guideline is not required. If this is not the case, then an assessment per this guideline is expected.

4.2 Post-Approval Changes to the Drug Product Chemistry, Manufacturing, and Controls

Post-approval submissions involving the drug product (e.g., change in composition, manufacturing process, dosage form) should include an evaluation of the potential risk associated with any new mutagenic degradation products or higher acceptance criteria for existing mutagenic degradation products. If appropriate, the regulatory submission would include an updated control strategy. Reevaluation of the drug substance associated with drug products is not recommended or expected provided there are no changes to the drug substance. Changing the site of manufacture of drug product will not require a reassessment of mutagenic impurity risk.

4.3 Changes to the Clinical Use of Marketed Products

Changes to the clinical use of marketed products that can warrant a reevaluation of the mutagenic impurity limits include a significant increase in clinical dose, an increase in duration of use (in particular when a mutagenic impurity was controlled above the lifetime acceptable intake for a previous indication that may no longer be appropriate for the longer treatment duration associated with the new indication), or for a change in indication from a serious or life threatening condition where higher acceptable intakes were justified (Section 7.5) to an indication for a less serious condition where the existing impurity acceptable intakes may no longer be appropriate. Changes to the clinical use of marketed products associated with new routes of administration or expansion into patient populations that include pregnant women and/or pediatrics will not warrant a reevaluation, assuming no increases in daily dose or duration of treatment.

4.4 Other Considerations for Marketed Products

Application of this guideline may be warranted to marketed products if there is specific cause for concern. The existence of impurity structural alerts alone is considered insufficient to trigger follow-up measures, unless it is a structure in the cohort of concern (Section 3). However a specific cause for concern would be new relevant impurity hazard data (classified as Class 1 or 2, Section 6) generated after the overall control strategy and specifications for market authorization were established. This new relevant impurity hazard data should be derived from high-quality scientific studies consistent with relevant regulatory testing guidelines, with data records or reports readily available. Similarly, a newly discovered impurity that is a known Class 1 or Class 2 mutagen that is present in a marketed product could also be a cause for concern. In both of these cases when the applicant becomes aware of this new information, an evaluation per this guideline should be conducted.

5. Drug Substance and Drug Product Impurity Assessment

Actual and potential impurities that are likely to arise during the synthesis and storage of a new drug substance, and during manufacturing and storage of a new drug product should be assessed.

The impurity assessment is a two-stage process:

- Actual impurities that have been identified should be considered for their mutagenic potential.
- An assessment of potential impurities likely to be present in the final drug substance is carried out to determine if further evaluation of their mutagenic potential is required.