製薬協

ICH E8「臨床試験の一般指針」改訂（案）説明会

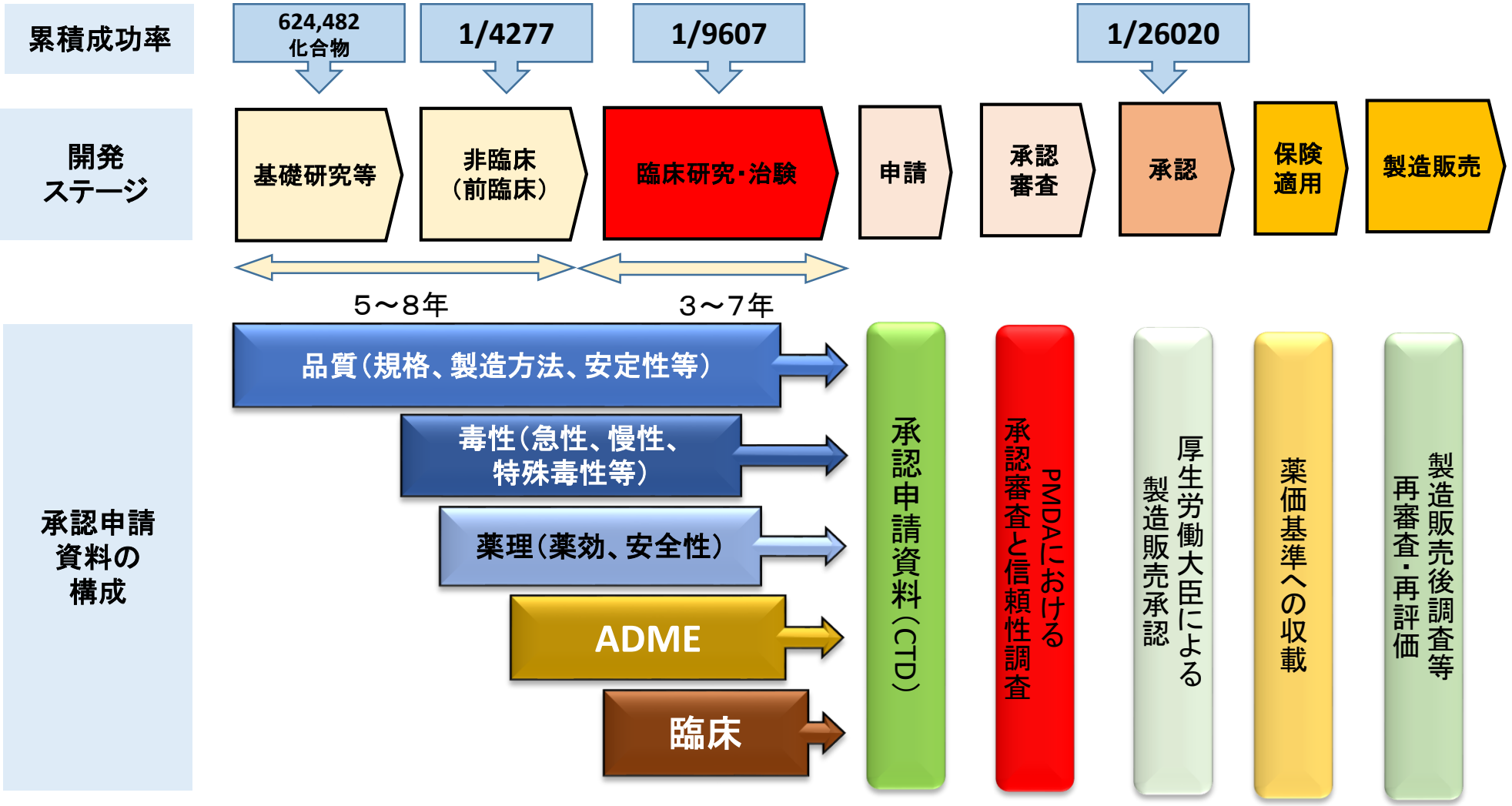
# ICH E8 （R1）ガイドラインへの期待
# 製薬企業の立場から

2019年7月25日
よみうりホール

日本製薬工業協会　医薬品評価委員会　臨床評価部会
近藤　充弘

# 医薬品の研究・開発

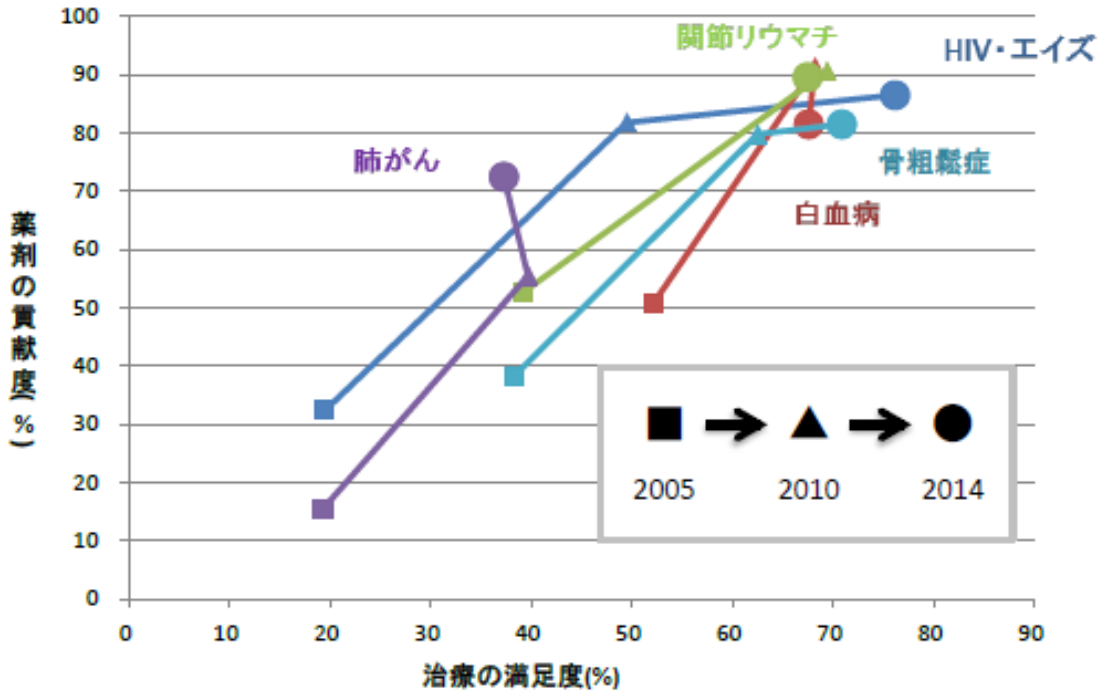
（参考：製薬協DATA BOOK 2019）




**製薬協　集計では、上市した1医薬品あたり、**
**研究開発費は500億円、販売促進費等を含めた総費用は1,200～1,900億円**

# 疾患治療における薬剤貢献度の推移

- 革新的な医薬品の創出により、生活習慣病における治療満足度が高水準に到達
- 各種のがん、HIV・エイズ、関節リウマチ、骨粗鬆症等の治療における薬剤貢献度もこの10年間で大幅に向上している




注：治療満足度は、各疾患に関するアンケート調査において、「十分満足のいく治療がおこなえている」「ある程度満足のいく治療がおこなえている」との回答合計の割合
薬物貢献度は、同調査の各疾患への医薬品の治療への貢献度において「十分に貢献している」「ある程度満足貢献している」との回答合計の割合
出典：公益財団法人ヒューマンサイエンス振興財団.「平成26年度国内基盤技術調査報告書　60疾患の医療ニーズ調査と新たな医療ニーズ」(2015年3月)をもとに作成

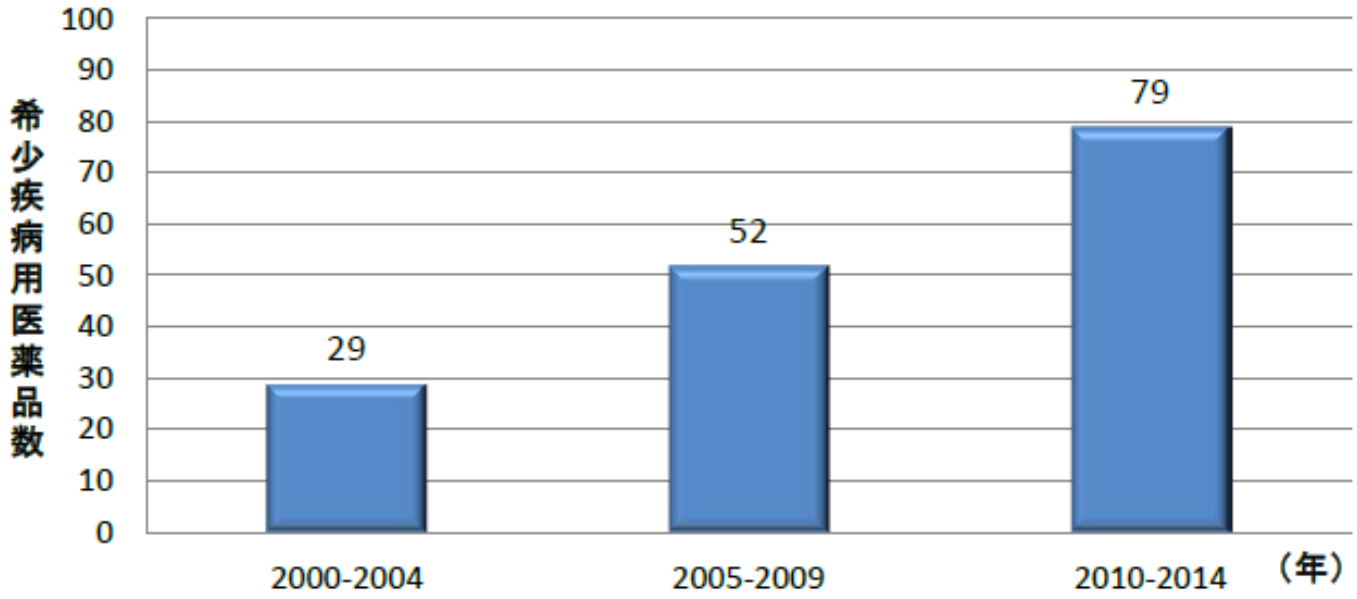
製薬協 産業ビジョン2025参考資料より

製薬協

製薬協 産業ビジョン2025
世界に届ける創薬イノベーション
ビジョン1

# 希少疾病用医薬品 承認数の推移

国内の希少疾患治療薬の承認数は、2000～2004年の29品目から継続的に増え、2005～2009年は52品目、2010～2014年は79品目となっている




出典：医薬産業政策研究所.「日本における新薬の臨床開発と承認審査の実績－2000～2014年承認品目－」リサーチペーパー・シリーズ No.68（2015年11月）より作成

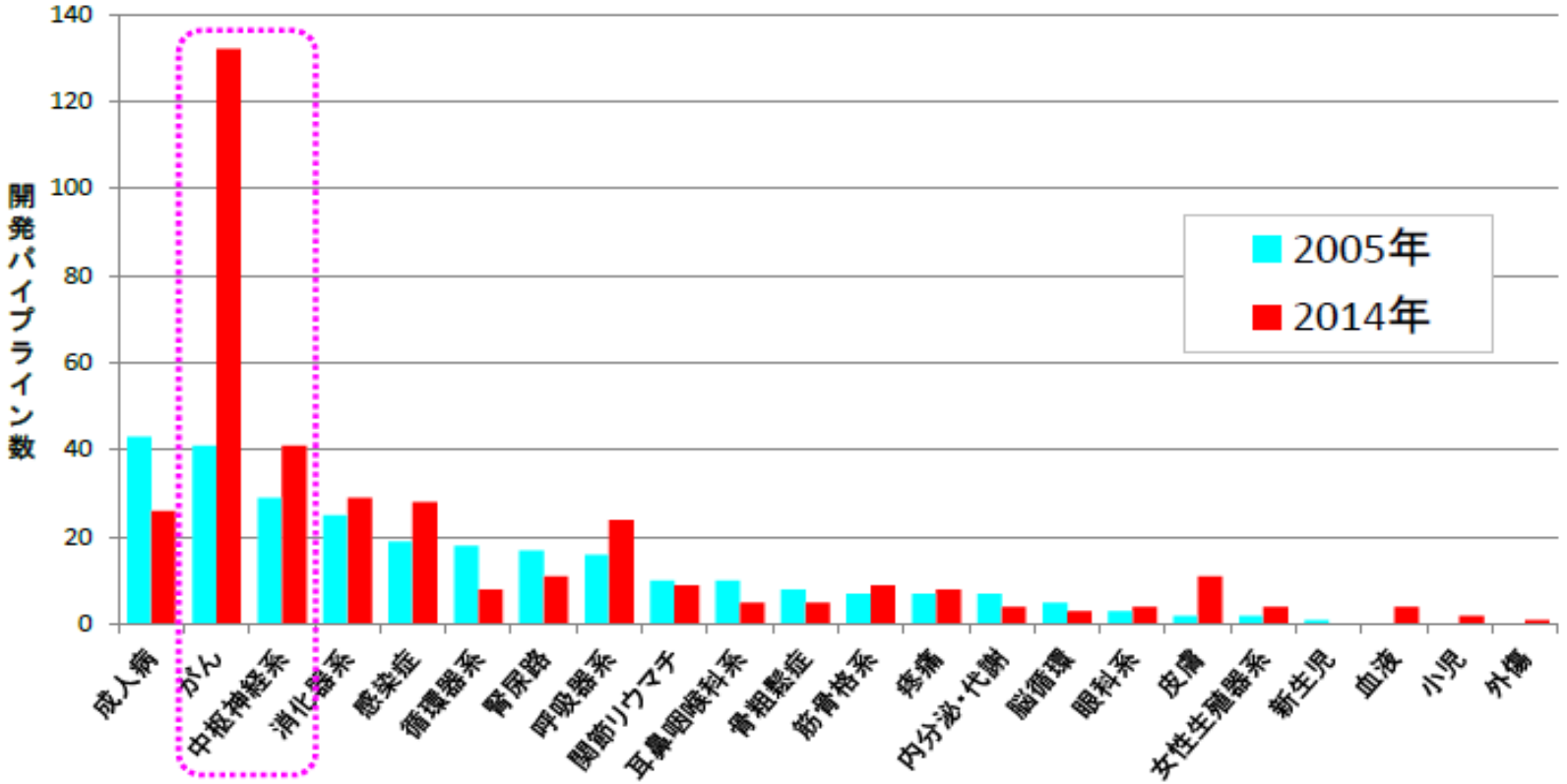
製薬協 産業ビジョン2025参考資料より

# アンメットメディカルニーズの高い疾患に対する医薬品開発状況

製薬協 産業ビジョン2025
世界に届ける創薬イノベーション
ビジョン1

製薬協

製薬協会員会社の医薬品開発状況では、アンメットメディカルニーズの高いがん、中枢神経系領域で、近年多くの医薬品が開発されている

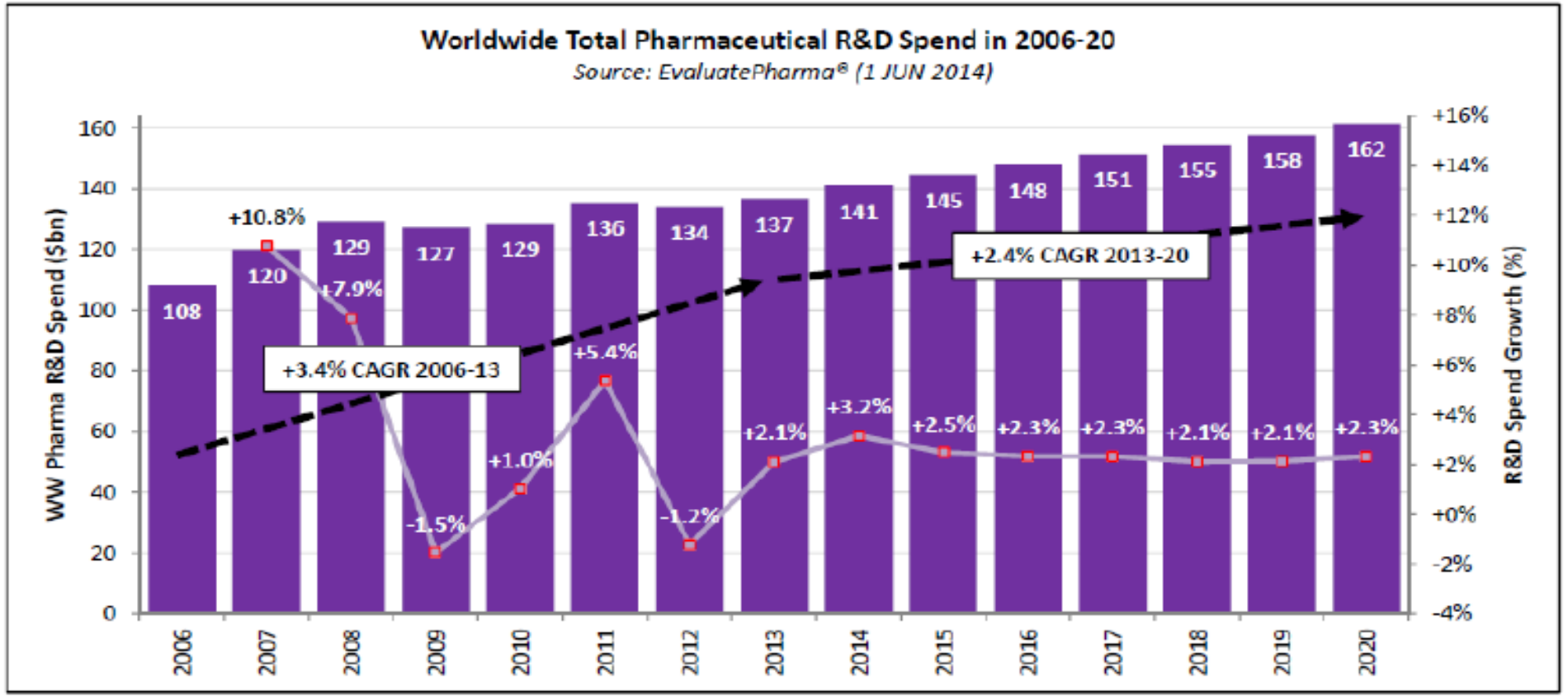



注：製薬協常任理事会社を対象
出所：各社公表資料および各社への聞き取り（製薬協調べ）

製薬協 産業ビジョン2025参考資料より

# 全世界の医薬品研究開発費

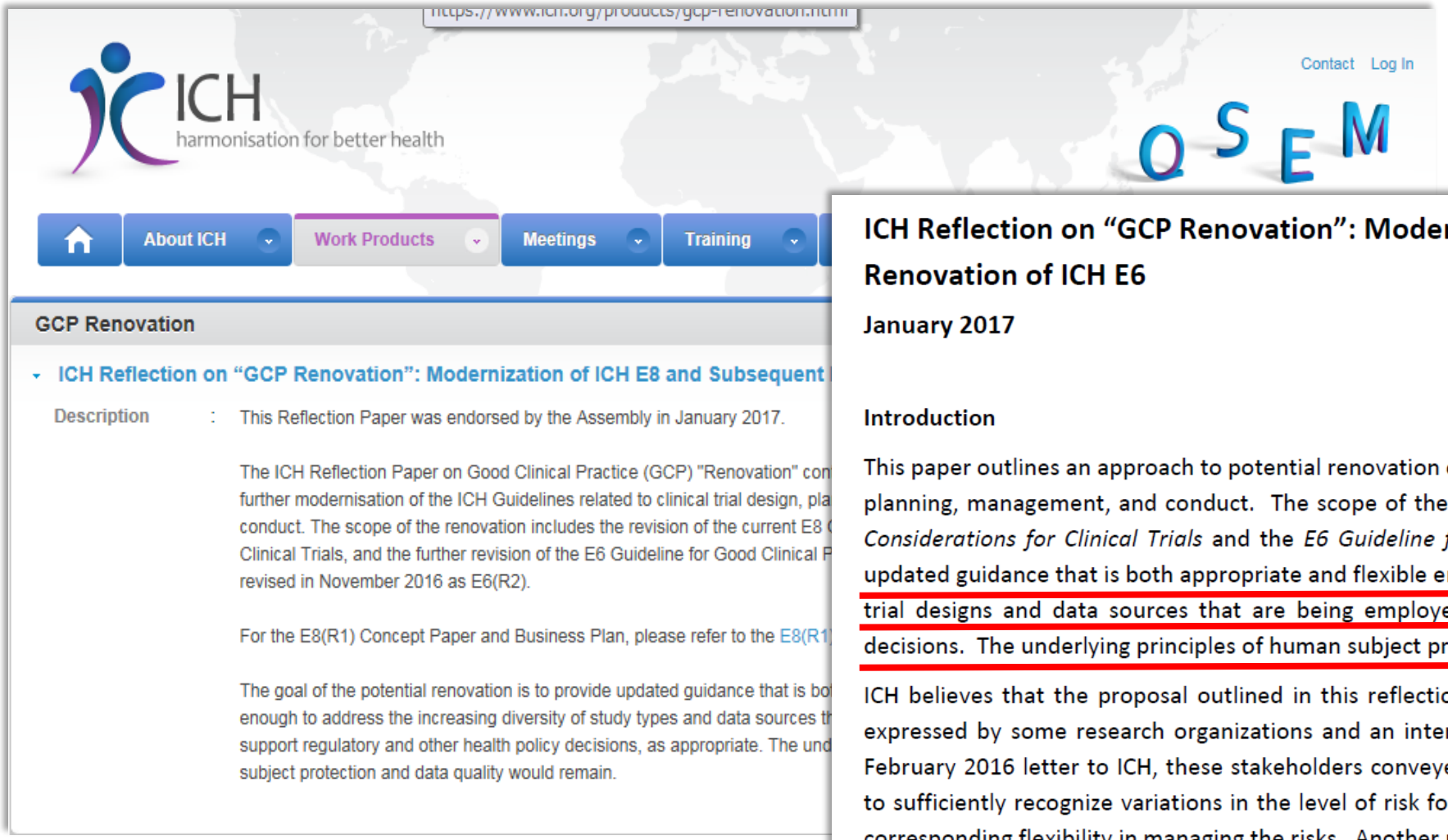
全世界の医薬品研究開発費は、2013年から2020年まで年平均2.4%で拡大し、1620億米ドルに達するとの予測されている




出典：EvaluatePharma. "World Preview 2014, Outlook to 2020"（2014年6月）

製薬協 産業ビジョン2025参考資料より

# GCP Renovationのインパクト




**ICH Reflection on "GCP Renovation": Modernization of ICH E8 and Subsequent Renovation of ICH E6**

**January 2017**

**Introduction**

This paper outlines an approach to potential renovation of the ICH Guidelines related to clinical trial design, planning, management, and conduct. The scope of the renovation would include the current *E8 General Considerations for Clinical Trials* and the *E6 Guideline for Good Clinical Practice*. The goal is to provide updated guidance that is both appropriate and flexible enough to address the increasing diversity of clinical trial designs and data sources that are being employed to support regulatory and other health policy decisions. The underlying principles of human subject protection and data quality would remain.

ICH believes that the proposal outlined in this reflection paper would largely address concerns recently expressed by some research organizations and an international consortium of health researchers.[1] In a February 2016 letter to ICH, these stakeholders conveyed concerns that the current ICH E6 guideline fails to sufficiently recognize variations in the level of risk for participants in different types of trials and allow corresponding flexibility in managing the risks. Another major concern was related to E6's limited scope. It was felt that a guideline entitled "good clinical practice" should more holistically address the planning and conduct of clinical trials.

ICH Official HPより

# GCP Renovationのタイムラインイメージ

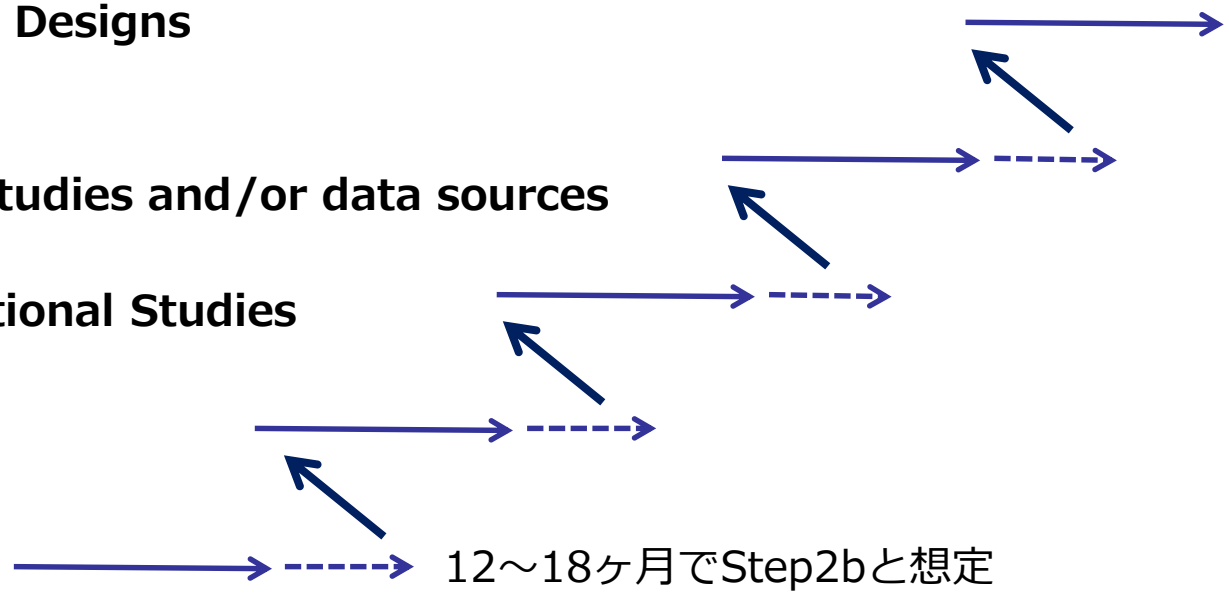
**E6 Annex3; Non-Traditional Trial Designs**

**E6 Annex2;**
**Non-Traditional Interventional Studies and/or data sources**

**E6 Annex1; Traditional Interventional Studies**

**E6 Overarching Principle**

**E8（R1）**



12～18ヶ月でStep2bと想定

E8 Modernization and GCP Renovation Reflection Paper パブコメ

2017　2018　2019　2020　2021　2022　2023　2024

E8（R1）：Step3（パブコメ中）
E6（R3）：11月ICH会議より議論開始

# E8(R1) Draft Guidelineと、臨床試験の一般指針（案）

| 1.OBJECTIVES OF THIS DOCUMENT | 1.本指針の目的 |
|---|---|
| 1.Describe internationally accepted principles and practices in the design and conduct of clinical studies that will facilitate acceptance of data and results by regulatory authorities | 1.規制当局によるデータと結果の受け入れを促進する、臨床試験のデザインと実施に関する国際的に受け入れられる原則と具体的なあり方を記述すること |
| 2. Provide guidance on the consideration of quality in the design and conduct of clinical studies across the product lifecycle, including the identification during study planning of factors that are critical to the quality of the study, and the management of risks to those factors during study conduct | 2.試験の計画段階での試験の質に関する重要な因子の同定と、試験実施中のそれら因子に対するリスクの管理を含む、医薬品（product）のライフサイクルを通じた臨床試験のデザインと実施に関する質の検討に関する指針を提供すること |
| 3.Provide an overview of the types of clinical studies performed during the product lifecycle, and describe the aspects of those studies that support the determination of which quality factors are critical to ensuring the protection of study subjects, the integrity of the data, the reliability of results, and the ability of the studies to meet their objectives | 3.医薬品のライフサイクルを通して実施される臨床試験の種類の概要を提供し、それら臨床試験について、試験の被験者の保護、データの完全性（integrity）、結果の信頼性及び試験の目的を達成するための能力を保証するためには質に関するどの因子が重要であるかの決定を支援するための側面を記述すること |
| 4. Provide a guide to the ICH efficacy documents to facilitate user's access | 4.有効性に関する ICHガイドラインへの利用者のアクセスを促進するため、ガイドを提供すること |

# 今後の取り組みを活性化させて

- 医薬品のライフサイクルを通した取り組み
- 目的に応じた試験デザイン/データソースの選択と実践
- Quality by Designの実践
- 患者を含む各ステークホルダーとの早期からの連携
- E6だけではなく、他のICH Efficacy Guidelineの実践

重要なポイントに注力可能となり、最終的に医薬品アクセスが向上

# 医薬品のライフサイクルを通した取り組み

4. DRUG DEVELOPMENT PLANNING （抜粋）

Efficient drug development usually requires appropriately planned interactions with regulatory authorities throughout development, both in relation to planning early as well as later studies including post-approval studies. This is particularly important for multiregional studies to ensure the study design is aligned with regional regulatory requirements.

A drug development plan describes all aspects of the development of a product from the target product profile through post-approval activities. The plan is usually prepared prospectively and updated as the development progresses and new information becomes available. The plan generally includes characterisation of formulation development, non-clinical studies required to support the evaluation of the product in human clinical studies and to support product approval, clinical studies designed to support the demonstration of efficacy and safety in the relevant patient population, studies in special populations (e.g., paediatric populations), regional considerations for product commercialisation (e.g., health technology assessments), and post-approval studies.

It is important to ensure that the experiences, perspectives, needs, and priorities of stakeholders relating to the development and evaluation of the drug throughout its lifecycle are captured and meaningfully incorporated into the development programme.

## ライフサイクル全体を通したDevelopment Planの作成と実践

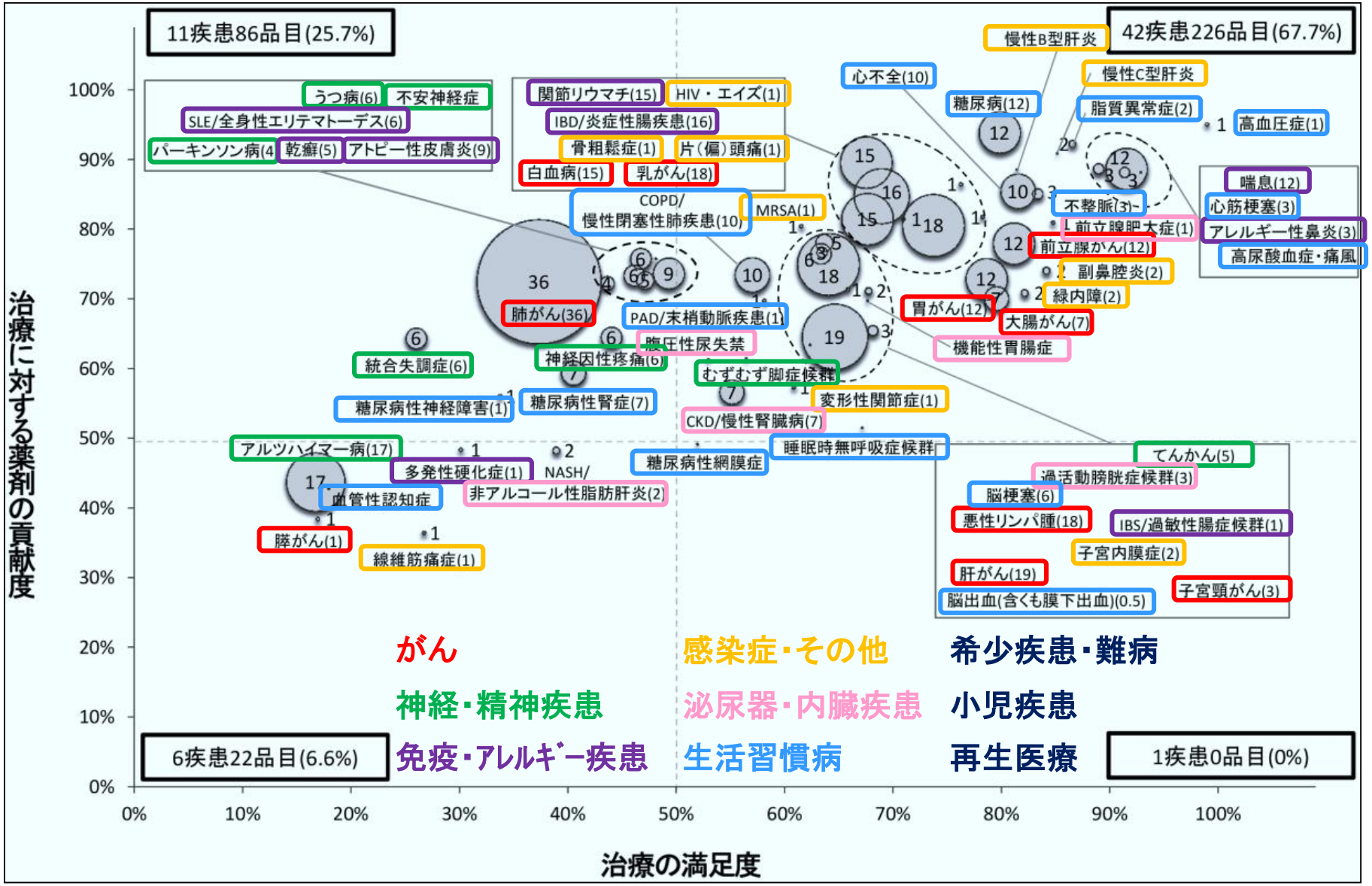
# 目的に応じた試験デザイン/データソースの選択と実践

5. DESIGN ELEMENTS FOR CLINICAL STUDIES

Study objectives impact the choice of study design and data sources, which in turn impact the strength of a study to support regulatory decisions and clinical practice. This section presents important elements that define the design of a clinical study. It is intended to assist in identifying the critical to quality factors necessary to achieve the study objectives and the protection of study subjects, while also enabling flexibility in study design and promoting efficiency in study conduct. This document does not discuss all possible study types that may be included within the drug lifecycle. The elements outlined here are expected to be relevant to study types and data sources in use in clinical studies now, and that may be developed in the future.
Clear objectives will help to determine the study design and conversely, the process of specifying the design may help to further clarify the objectives. Objectives may need to be modified as practical considerations and limitations are revealed.

## 目的に応じたデザイン/データソースを選択し柔軟性を持たせた実践

# 治療満足度・薬剤貢献度（2014年度）別にみた新薬開発件数（2017年6月時点）

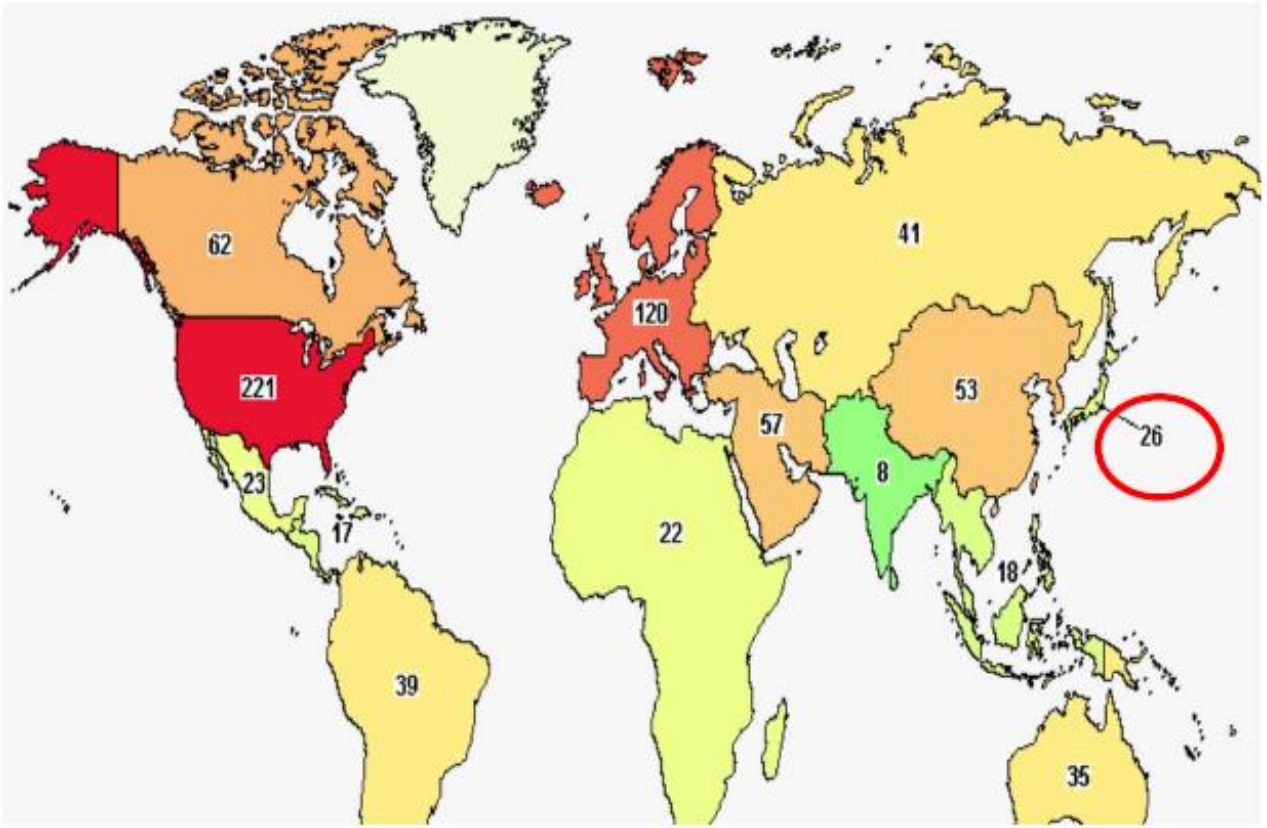



製薬会社20社の2017年6月時点における国内開発品目（60疾患334件）

引用：HS 財団による調査結果、各社公表情報、製薬協ホームページ、明日の新薬をもとに作成
「医薬産業政策研究所　政策研ニュース　No.52　2017年11月」を元に分類

# 小児医薬品開発状況

## 26* Industry-sponsored pediatric trials currently enrolling in Japan




Taken from
Clinicaltrials.gov search
Jun 25, 2019

Search Term: Pediatric
Funder Type: Industry
Study Status: Recruiting patients

https://www.clinicaltrials.gov/ct2/results/map?cond=pediatric&term=&cntry=&state=&city=&dist=&recrs=a

* Author acknowledges that this ct.gov data may not represent a full picture of total trial activities; provided here as an illustrative example

2019年7月12日開催「小児医薬品開発ワークショップ」 橋上氏スライドより

# Quality by Designの実践

3.1. Quality by Design of Clinical Studies

Quality is a primary consideration in the design, planning, conduct and analysis of clinical studies and a necessary component of clinical development programmes. The likelihood that a clinical study will answer the research questions posed in a reliable manner, meaningful for decision makers and patients, while preventing important errors, can be dramatically improved through prospective attention to the design of all components of the study protocol, procedures and associated operational plans.
Quality should rely on good design and its execution rather than overreliance on retrospective document checking, monitoring, auditing or inspection. These activities are an important part of a quality assurance process but are not sufficient to ensure quality of a clinical study.

3.2. Critical to Quality Factors

A basic set of factors relevant to ensuring study quality should be identified for each study. Emphasis should be given to those factors that stand out as critical to study quality. These critical to quality factors are attributes of a study whose integrity is fundamental to the protection of study subjects, the reliability and interpretability of the study results, and the decisions made based on the study results. These quality factors are considered to be critical because, if their integrity were to be undermined by errors of design or conduct, the reliability or ethics of decision-making would also be undermined.

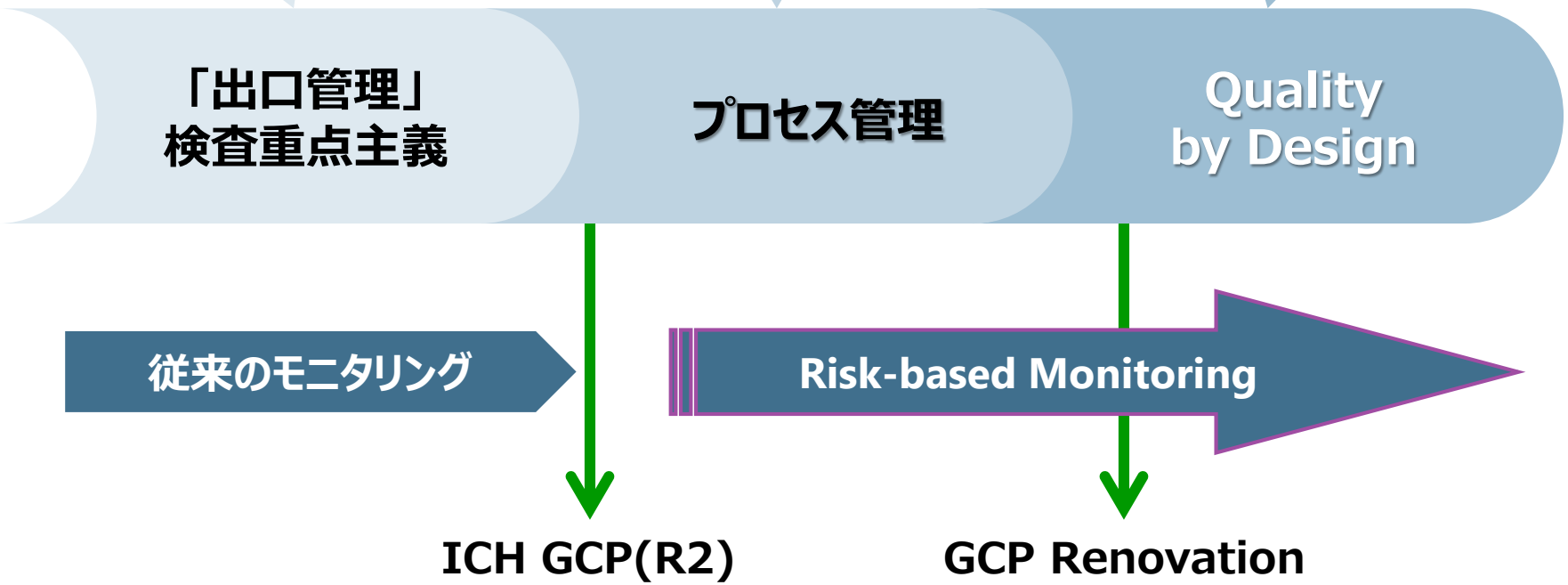
従来の質管理の発想からの脱却と実践

# 従来の手法からの脱却

できた不良品をはじく
厳格な出荷検査，
受け入れ検査が中心

**事後的な検査を不要**
にするための活動

プロセス管理を前提とした
**デザイン設計**




製薬協 小宮山氏資料一部改変

# 患者を含む各ステークホルダーとの早期からの連携

2.3 Patient Input into Study Design

Consulting with patients and/or patient organisations in the design, planning and conduct of clinical studies helps to ensure that all perspectives are captured. Patients' views can be requested on all phases of drug development. Involving patients at the early stage of study design is likely to increase trust in the study, facilitate recruitment, and promote adherence, which should continue throughout the duration of the study. Patients also provide their perspective of living with a condition, which contributes to the determination of endpoints that are meaningful to patients, selection of the right population, duration of the study, and use of the right comparators. This ultimately supports the development of medicines that are better tailored to patients' needs.

3.3.3 Engaging Stakeholders in Study Design

Clinical study design is best informed by input from a broad range of stakeholders, including patients and treating physicians. It should be open to challenge by subject matter experts and stakeholders from outside, as well as within, the sponsor organisation.

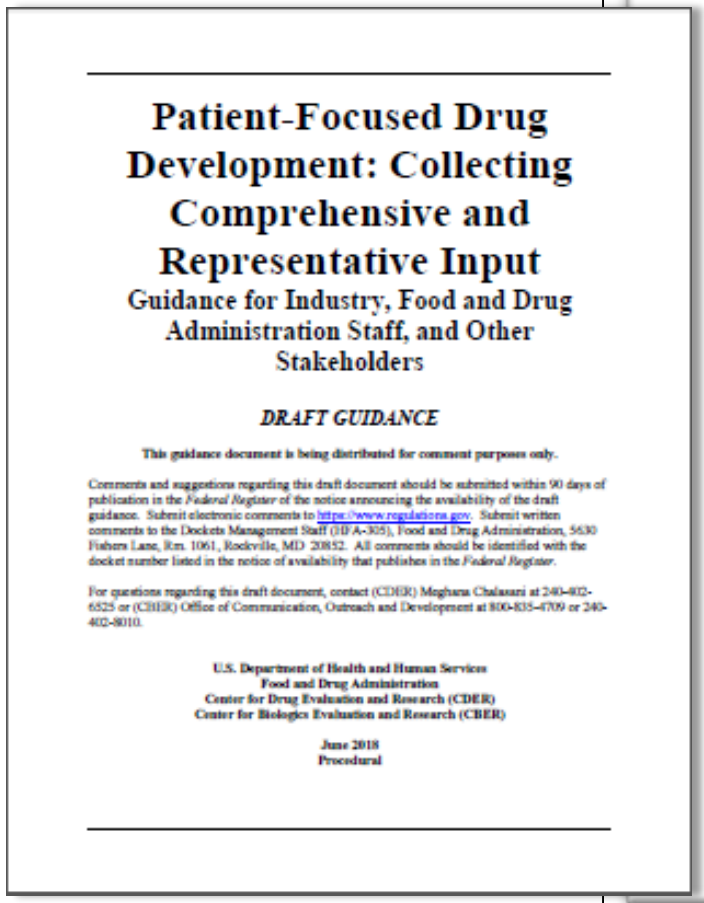
7. CONSIDERATIONS IN IDENTIFYING CRITICAL TO QUALITY FACTORS（最初のビュレット）

Engagement of all relevant stakeholders, including patients, is considered during study planning and design.

## 国内では遅れていた「産患官学連携」の実践と推進

# 患者参画の取り組み例

## FDA



Patient-Focused Drug Development: Collecting Comprehensive and Representative Input

Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

*DRAFT GUIDANCE*

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

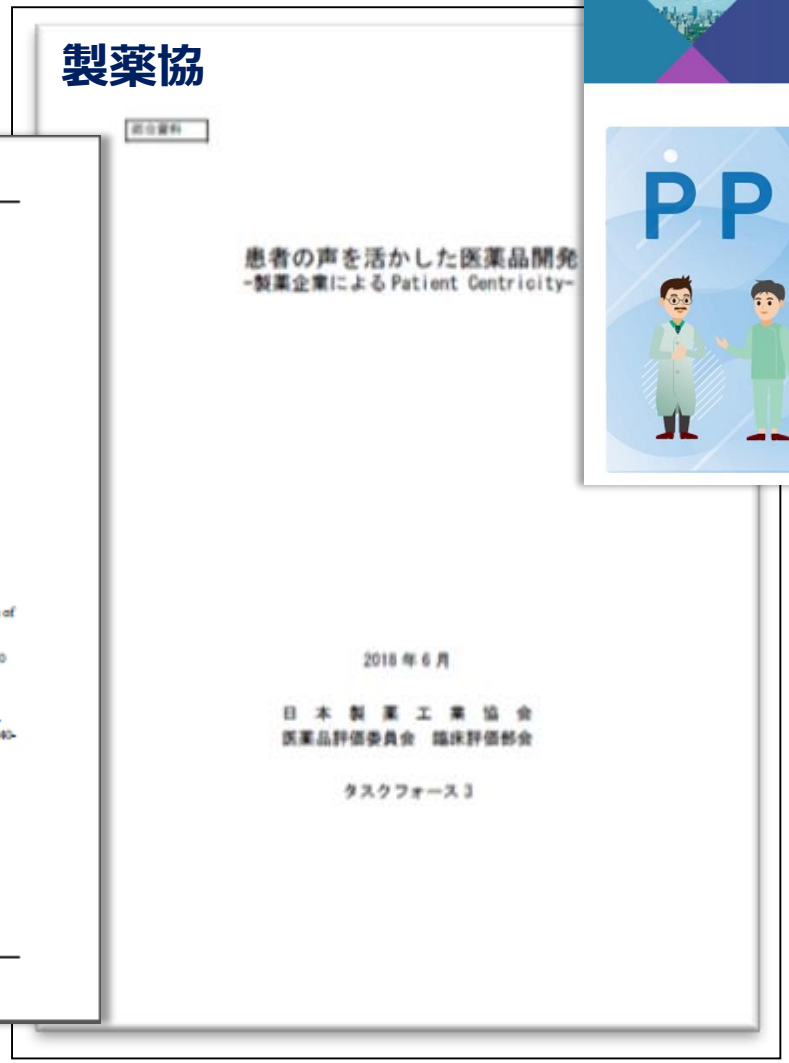
For questions regarding this draft document, contact (CDER) Meghana Chalasani at 240-402-6525 or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2018
Procedural

出典：「Patient-Focused Drug Development: Collecting Comprehensive and Representative Input」 FDA
https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm610442.pdf

## 製薬協



患者の声を活かした医薬品開発
-製薬企業による Patient Centricity-

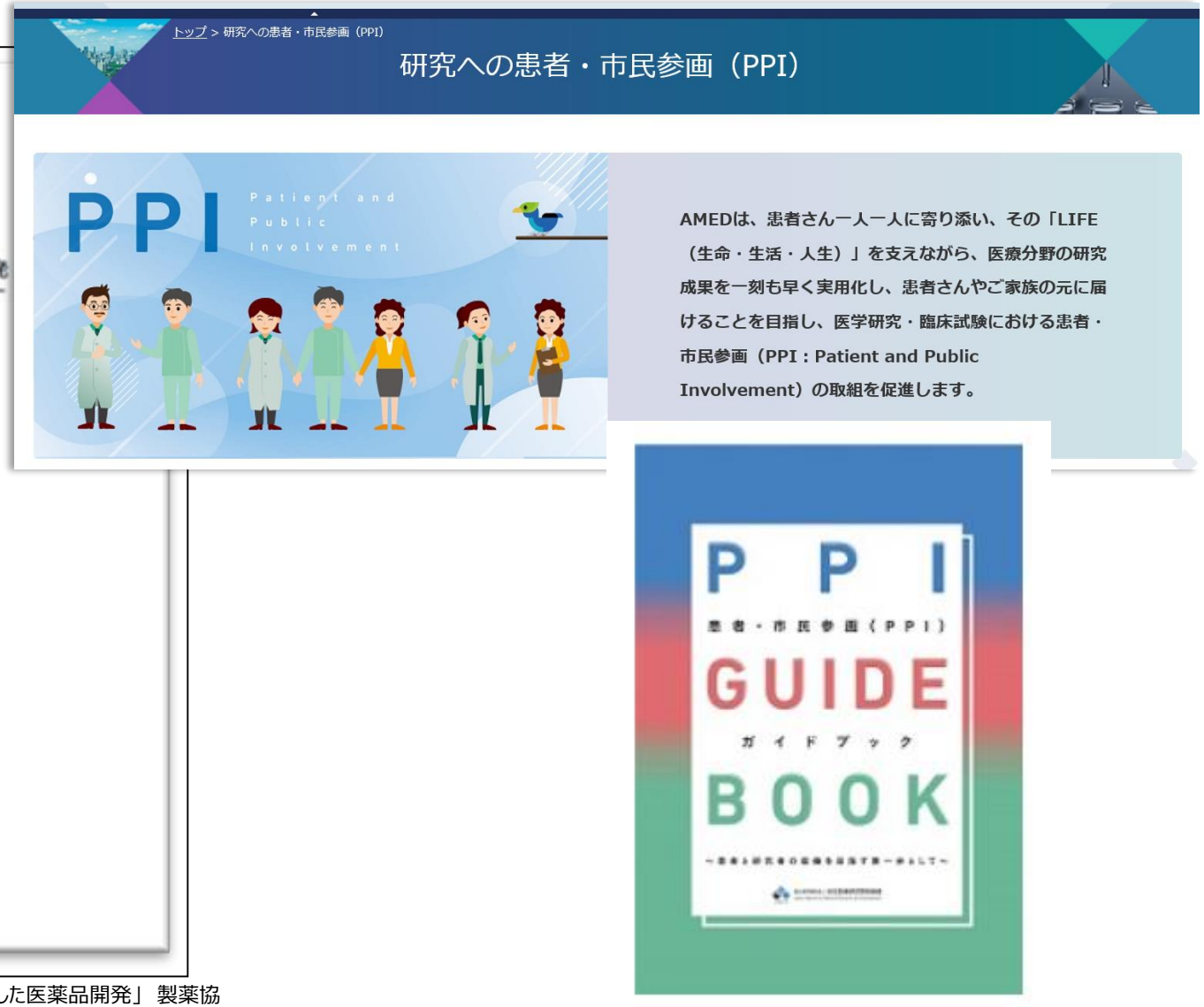
2018年6月

日本製薬工業協会
医薬品評価委員会　臨床評価部会

タスクフォース3

出典：「患者の声を活かした医薬品開発」 製薬協
（http://www.jpma.or.jp/medicine/shinyaku/tiken/allotment/patient_centricity.html）

## AMED




出典：「研究への患者・市民参画（PPI）」AMED
（https://www.amed.go.jp/ppi/index.html）

# 他のICH Efficacy Guidelineの実践

**E8 General Considerations for Clinical Trials**

**Design and analysis:**
E4 Dose-Response Studies
E9 Statistical Principles for Clinical Trials
E10 Choice of Control Group in Clinical Trials
E17 Multi-Regional Clinical Trials

**Conduct and reporting:**
E3 Clinical Study Reports
E6 Good Clinical Practice

**Safety reporting:**
E1 Clinical Safety for Drugs used in Long-Term Treatment
E2A - E2F Pharmacovigilance
E14 Clinical Evaluation of QT
E19 Safety Data Collection

**Populations:**
E5 Ethnic Factors
E7 Clinical Trials in Geriatric Population
E11 - E11A Clinical Trials in Pediatric Population
E12 Clinical Evaluation by Therapeutic Category

**Genetics/genomics:**
E15 Definitions in Pharmacogenetics / Pharmacogenomics
E16 Qualification of Genomic Biomarkers
E18 Genomic Sampling

グローバル開発の中での国内開発を推進するために、
関連する全てのICH Guidelineを効果的に実践

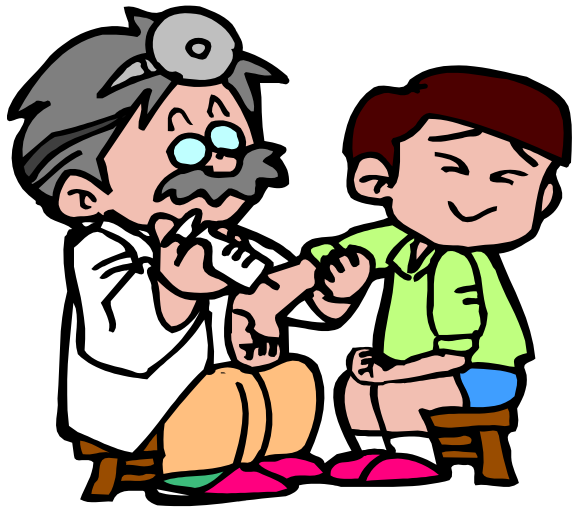
# 今後の取り組みの活性化・・・

- 医薬品のライフサイクルを通した取り組み
- 目的に応じた試験デザイン/データソースの選択と実践
- Quality by Designの実践
- 患者を含む各ステークホルダーとの早期からの連携
- E6だけではなく、他のICH Efficacy Guidelineの実践

被験者保護、結果の信頼性確保を大前提に、
目的に応じて重要なポイントに注力し、
最終的に医薬品アクセスを向上

製薬協

# ご清聴ありがとうございました



より良い医薬品をより早く
患者さんのもとに