中国における抗がん剤開発　今と昔

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Clinical Development Services,
Covance

第8回がん新薬開発合同シンポジウム
(Tokyo, 5 Oct 2018)

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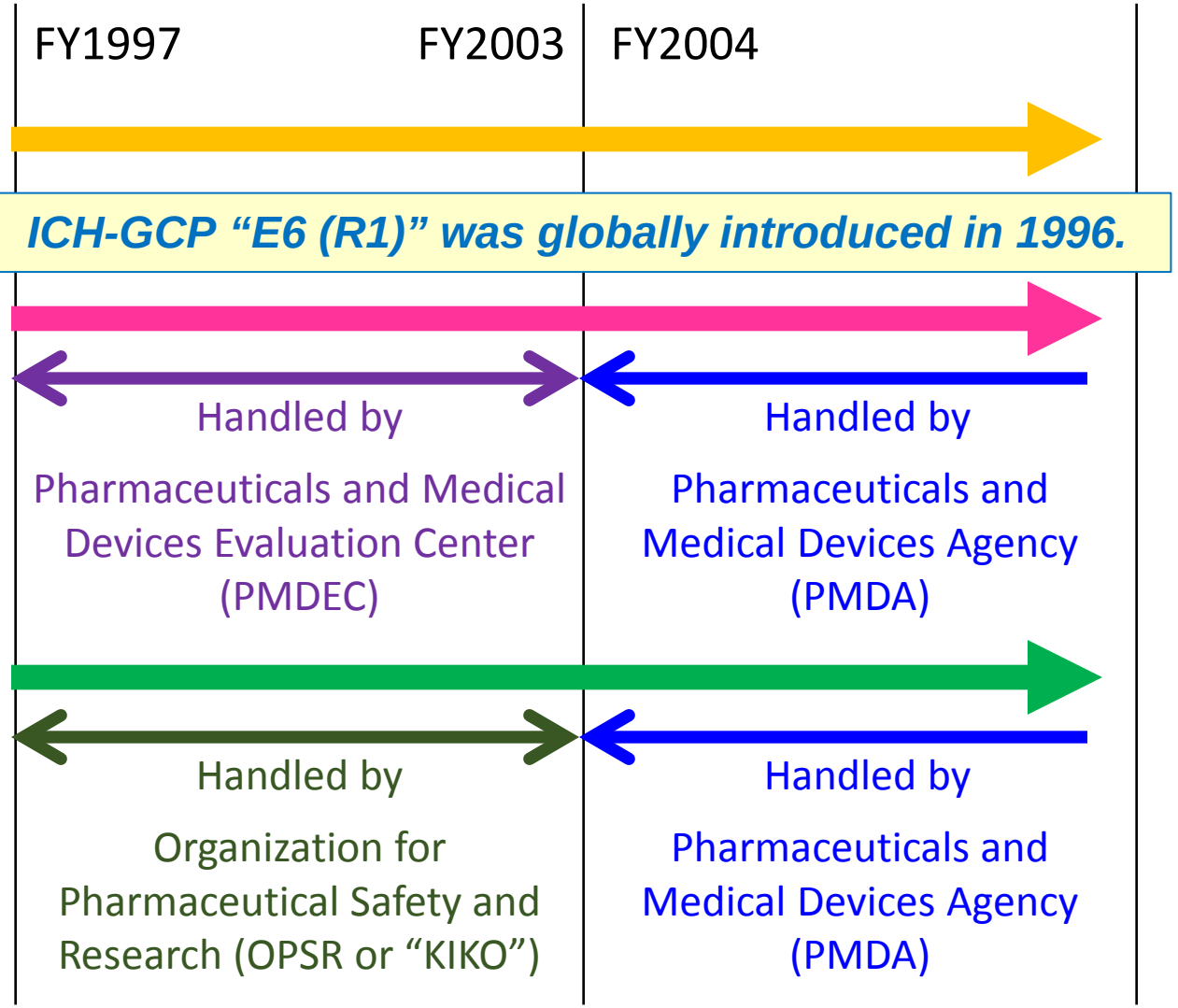
Histories of ICH-GCP Implementation, Clinical Trial Notification, and Clinical Trial Consultation in Japan



In East Asia, the ICH GCP was adopted in Japan in 1997, in Korea in 2001, in Taiwan in 2002, and in China in 2003 respectively.

Tetsuomi Takano, Covance Japan (Tokyo, 17/Jan/2018)

医薬品登録管理弁法 (SFDA局令第28号, 2007/10/1施行)
第44条　国際共同治験　←2002/12/1施行の試行版より記載有り

第四十四条　国外の申請者が中国で国際多施設共同臨床試験を行う場合、本弁法に従って国家食品薬品監督管理局に申請し、かつ以下の要件に沿うものとする。

（一）臨床試験被験薬は既に国外で登録された医薬品、または第Ⅱ相か第Ⅲ相臨床試験に入った医薬品でなければならない。国家食品薬品監督管理局は、国外申請者が提出する国外で未登録の予防用ワクチンに対する国際多施設共同臨床試験の申請を受理しない、

（二）国家食品薬品監督管理局は、国際多施設共同臨床試験を許可すると同時に、申請者に対し、先に中国で第Ⅰ相臨床試験を実施するよう要求することができる、

（三）中国において国際多施設共同臨床試験を行う時、いずれかの国において当該医薬品に関わる重篤な副作用と予期せぬ副作用が発見された場合、申請者は関連規定に基づき、直ちに国家食品薬品監督管理局に報告しなければならない、

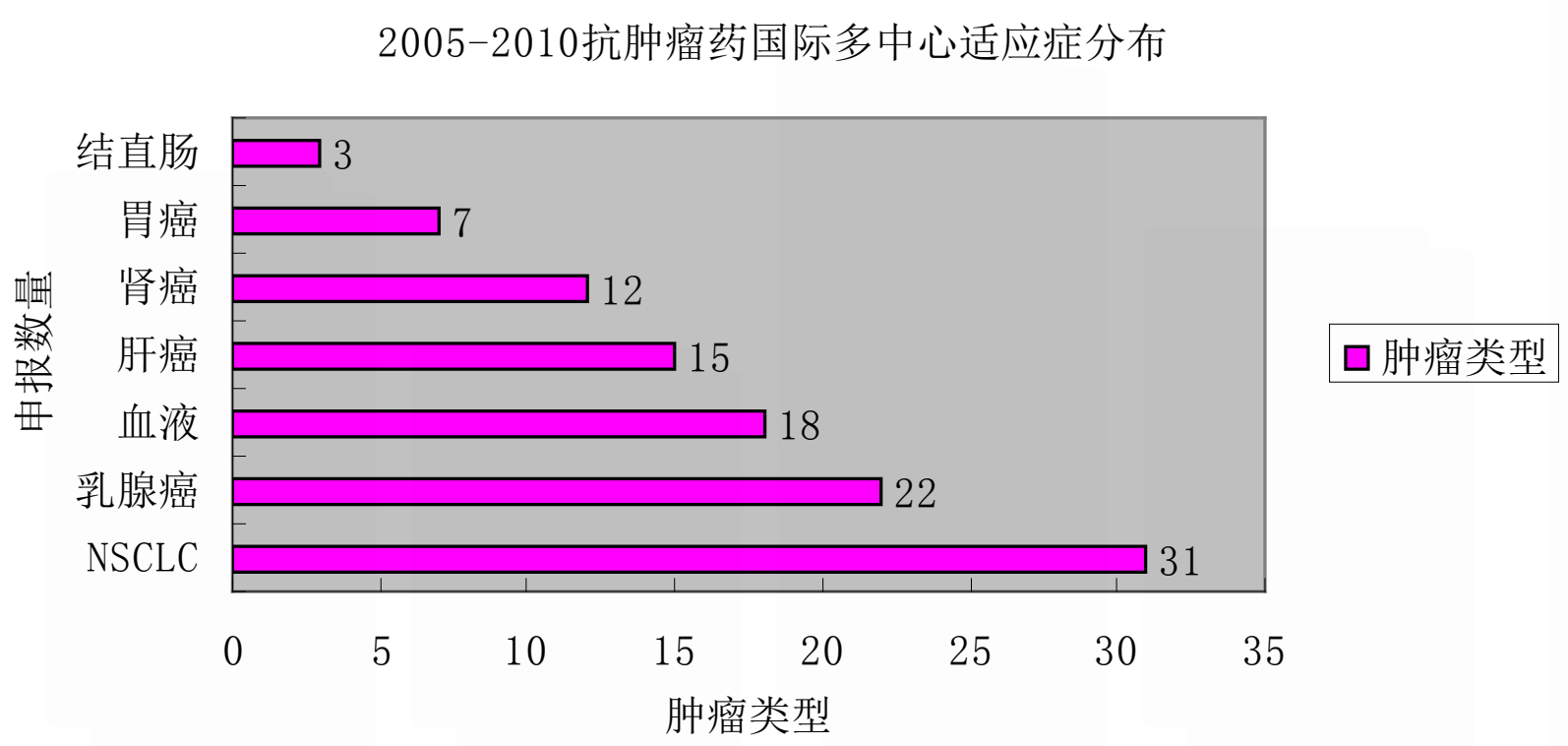
（四）臨床試験の終了後、申請者は完全な臨床試験報告書を国家食品薬品監督管理局に提出する、

（五）国際多施設共同臨床試験で取得したデータを中国での医薬品登録申請に使用する場合、本弁法の臨床試験に関する規定に適合しなければならない。同時に、申請者は国際多施設共同臨床試験の全研究資料を提出する。

- かつて国産薬のMRCTは認められていなかった。
- かつて輸入薬のP1(～P2)のMRCTに中国を参加させることはできなかった。

◊2005-2010.12

◊**Global clinical trial applications of small molecular products**



***2005-2010.12 total applications of small molecular products on oncology were 152. 123 of them were approved.**

Yang Zhimin, CDE, SFDA, China (APEC MRCT Tokyo Workshop, 02/Nov/2011)

RDPAC Member List

- Abbott
- AbbVie
- Allergan
- Amgen
- Astellas
- AstraZeneca
- Baxter
- Bayer HealthCare
- Boehringer Ingelheim
- Bristol Myers Squibb
- Celgene
- Chiesi
- Chugai
- Eisai
- Eli Lilly
- Ethypharm
- Fresenius Kabi
- Gedeon Richter
- Gilead
- GSK
- Helsinn
- Ipsen
- Kyowa Kirin
- LEO Pharma China
- Lundbeck
- Menarini
- Merck Serono
- MSD
- Mundipharma
- Novartis
- Novo Nordisk
- Pfizer
- Roche
- Sanofi
- Servier
- Shire
- Sumitomo
- Takeda
- UCB
- Xian-Janssen
- Zambon

Date Updated: September 2017

- Under the China Association of Enterprises with Foreign Investment (CAEFI), the R&D-based Pharmaceutical Association Committee (RDPAC) is a non-profit organization made up of 40 member companies with pharmaceutical R&D capability.
- RDPAC is member of International Federation of Pharmaceutical Manufacturers & Associations (IFPMA).

(Source: RDPAC website)

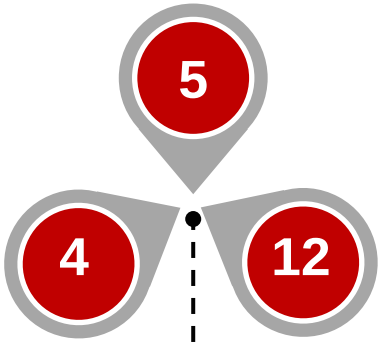
Outline of the Opinions of the State Council on Reforming the Evaluation and Approval System for Drugs and Medical Devices (State Council Doc 2015 No.44, 18/Aug/2015) and the China Regulatory Reform

Chinese government website: http://www.gov.cn/zhengce/content/2015-08/18/content_10101.htm
Japanese translation by CCFDIE: http://www.cjpi.org.cn/zryyxxwjp/zxdt/webinfo/2017/01/1485778118968067.htm
http://www.cjpi.org.cn/zryyxxwjp/scxx/zhxx/webinfo/2015/08/1485778130567129.htm

李克强
Lǐ Kèqíang
(01/Jul/1955-)

3-year reform plan initiated by China's State Council to reform the evaluation and approval system for drugs and medical devices since August 2015

Key Objectives



Safeguard Measures

Major Tasks

Key Objectives

- Improve the quality of review and approval
- Resolve the backlog of registration applications
- Improve the quality of generic drugs
- Encourage research and innovation
- Increase review and approval transparency

Faster and more improved & transparent processes for innovative drugs

5 new registration categories for chemical drugs were defined in Mar 2016.

Still updating; still partially under discussion and unclear; need close observation and discussion

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第12次5カ年計画(2011-2015)

2011年、中国政府は第12次5カ年計画(2011-2015)でバイオ医薬品産業を国家の基幹産業に育成すると発表

中国政府方針

- ❑ 高度先進技術のバイオ医薬品産業を育成し、中国発の大型新薬開発を進める
- ❑ 世界の工場から、世界の市場、世界の研究機関の中心へ
- ❑ 人材育成 (大学・研究機関を充実させ、優秀な人材の育成・海外の人材招聘)
- ❑ 新しい製品・技術の開発と導入 (原材料輸出から付加価値の高い 製品輸出へ転換)

政府主導の支援政策

- ❑ バイオ医薬は重点発展分野に入る、2020年までバイオ医薬強国を目指す
- ❑ バイオ医薬技術企業に対し減税(研究費用50%免税、所得税15%まで下げる)
- ❑ 第十二期五ヶ年計画（2011-15年）期間中、バイオ新薬の開発に400億元資金を投入予定

[出典：正田豊, 中国における医療制度改革と医療行政 (東京, 2012/7/10)]

第13次5カ年計画(2016-2020)

バイオ医薬品産業は、以後数年間で中国政府の重点支援を受けて急成長

- ➢ 2010年～2014年のバイオ医薬品産業における製造業の売上高の年平均成長率は23%以上
- ➢ 2020年には中国のバイオ医薬品市場は米国に次いで世界第2位へ

Founded in 1988, China Pharmaceutical Innovation and Research Development Association (PhIRDA) is registered as a non-profit organization by the Ministry of Civil Affairs of China at the first national level.

- PhIRDA will exert great effort on “academia-industry collaboration”, which centers on the principle of “innovation, industrialization, internationalization”, persists in innovation to achieve unmet clinical requirements.
- At current stage, PhIRDA has 142 members, mainly consist of five major categories: First, start-up and R&D enterprises focusing on innovation of pharmaceutical products; Second, domestic first-class universities, colleges and research institutions conducting pharmaceutical research and development; Third clinical institutions featuring high skills in applicable research on new drugs, especially those undertake “major new drug innovation” technological platform for good clinical practice; Fourth, investment institutions committing to pharmaceutical innovation; Fifth, national pharmaceutical enterprises excelling at innovation.
- PhIRDA is also a member of International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) to continuously broaden channels of international collaboration.

(Source: PhIRDA website)

- China BioMed Innovation and Investment Conference (CBIIC) was established on November 14, 2016 by China Pharmaceutical Innovation and Research Development Association (PhIRDA), China Association for Medical Devices Industry (CAMDI) and Hong Kong Exchange and Clearing Limited (HKEX).
- Aiming to build an authorized platform of collaboration and integration for pharmaceutical innovative enterprises, investors and capital at home and abroad, CBIIC has drawn more than 3500 participants, over 700 pharmaceutical industries and 500 financial institutions, including government officials, senior executives and experts in pharmaceutical industry and representatives from media.

Source: http://2018cbiic.phirda.com/

Announcement on Pilot Program of Drug MAH (Marketing Authorization Holder) System

The MAH pilot program in China has been started since 06/Jun/2016. JP Pharmas should also need to consider the next step.

[Extract from EN Translation for the announcement from the General Office of the State Council No. [2016] 41 (Released on 06/Jun/2016)]
http://www.gov.cn/zhengce/content/2016-06/06/content_5079954.htm

- Pilot Scope
  - Districts: *10 provinces or municipalities* including Beijing 北京, Tianjin 天津, Hebei 河北, Shanghai 上海, Jiangsu 江蘇, Zhejiang 浙江, Fujian 福建, Shandong 山東, Guangdong 広東, and Sichuan 四川
  - Pharmaceutical Products:
    It covers chemical drugs, biological products, traditional Chinese medicines and natural drugs.
    ① New drugs: According to current DRR chemical drugs registration category 1-4, part of category 5; biological products registration category 1, 7 and biosimilar; new registration category of chemical drugs 1-2
    ② Generic drugs approved based on the new standard of quality and efficacy consistent evaluation with original drugs: New registration category of chemical drugs 3-4
    ③ Marketed pharmaceutical products: Have passed the consistency evaluation; manufacturing site change.
- Pharmaceutical research and development institution or researcher in the Districts can be a MAH.
- Submission documents: Qualification certificates, drug qualify and safety responsibility commitment
- Obligations and responsibilities of MAH and contracted manufacturer
- Application of MAH
  - Newly registered products: Simultaneous application for being MAH with NDA
  - Marketed products: Supplemental application for being MAH and contracted manufacturing
- Implementation period is from Jun. 6, 2016 to Nov. 4, 2018.
- Drug manufacturers in the Districts can implement by referring to the requirements on MAH in the pilot program.

E-Journal on Requirements of Clinical Part Documents for FIH Clinical Trial Application of Oncology New Drugs

(by Chen Xiaoyuan, CDE; Released by CDE on 08 Feb 2018)

- Background: Oncology new drugs are hot spots for global innovation drug research, accounting for approximately 40% of current innovation drug clinical trial applications. However, at the present stage of the FIH application for oncology drugs, the submitted clinical trial programs had some problems such as uneven levels, lack of important content, and poor program operability. In order to encourage innovation and practical implementation of the "Opinions" of the two offices, the Chemical Clinical I Department of CDE has discussed the preparations for the application of clinical data for the first-in-human clinical trials of oncology new drugs.

- General Requirements:
  1. Overall R&D Plan
  2. Clinical Study Protocol (2.1 – 2.18)
  3. Clinical Study Protocol Supporting Documents
     (3.1 Overall Clinical Summary, 3.2 Independent Risk Management Plan, 3.3 IB, 3.4 ICF, 3.5 EC status, 3.6 Others)

CDE website: http://www.cde.org.cn/dzkw.do?method=largePage&id=314311

(Supported by RDPAC for English translation)

E-Journal on General Requirements of NDA/BLA Dossier for Anti PD-1/PD-L1 Monoclonal Antibody

(by Zhang Hong, CDE; Released by CDE on 08 Feb 2018)

- Including the 5 anti-PD-1/PD-L1 monoclonal antibodies marketed worldwide [Keytruda (Pembrolizumab), Opdivo (Nivolumab) / Tecentriq (Atezolizumab), Bavenci (Avelumab) and Imfinzi (Durvalumab)], there have been 16 similar products in China to obtain clinical approval, and carry out clinical trials in different tumor types. However, as of now, no anti-PD-1 or PD-L1 monoclonal antibody has been approved in China.

- CDE held a symposium on relevant product application information requirements in Beijing on 12 Jan 2018. To meet urgent unmet medical needs of advanced cancer patients, shorten NDA/BLA review periods, and accelerate market access of anti-PD-1/PD-L1 monoclonal antibodies in China, CDE would newly initiate accelerate approval with surrogate endpoint of Objective Response Rate (ORR) and rolling submission system at NDA/BLA review stage for the first time in China. Actual procedures for each NDA/BLA product of anti-PD-1/PD-L1 monoclonal antibodies will be discussed at Pre-NDA meeting between CDE and sponsor/applicant.

- Detailed Requirements for Rolling Submission Dossiers at (I) Initial submission, (II) During the NDA review, and (III) Final submission before NDA approval were also disclosed on the CDE website.

CDE website: http://www.cde.org.cn/dzkw.do?method=largePage&id=314347

(Supported by RDPAC for English translation)

“CAR-T” and “recruiting or not yet recruiting” at ClinicalTrials.gov (as of 12 Sep 2018)

Country/ Region	# of studies
Japan	1
China	156
Hong Kong	0
Taiwan	1
Korea	0
Singapore	1
Australia	2

Country/ Region	# of studies
UK	9
France	12
Germany	4
Swiss	2
Italy	6
Spain	8
Sweden	1
Russia	1

Country/ Region	# of studies
US	121
Canada	18
Brazil	4
South Africa	3

(Source: ClinicalTrials.gov)

Preliminary List of Expert Advisory Committee for Drug Registration Review (Chemical and Biological Drugs No. 38-35: Oncology Experts)

(Draft; Released by CDE on 29 Dec 2017 for Public Comment till 09 Jan 2018)

- The establishment of 38 expert advisory committees with each number of experts was proposed.
- The preliminary list of 630 experts was announced (Attachment 2).

1	马 军	哈尔滨血液病肿瘤研究所
2	**王建祥**	中国医学科学院天津血液病研究所白血病诊疗中心
3	**毛**颖	复旦大学附属华山医院神经外科
4	**石**远凯	中国医学科学院肿瘤医院内科
5	卢铀	四川大学华西医院胸部肿瘤科
6	**江**泽飞	军事医学研究院附属医院乳腺肿瘤科
7	**吴炅**	复旦大学附属肿瘤医院乳腺外科

8	**吴一**龙	广东省人民医院肺癌研究所
9	**沈琳**	北京大学肿瘤医院消化肿瘤内科
10	**郎**锦义	四川省肿瘤医院肿瘤放疗中心
11	**秦叔逵**	解放军南京八一医院全军肿瘤中心
12	**徐兵河**	中国医学科学院肿瘤医院内科
13	**徐瑞**华	中山大学肿瘤医院内科
14	**郭**军	北京大学肿瘤医院肾癌黑色素瘤内科
15	韩**宝惠**	上海市胸科医院呼吸内科

CDE website: http://www.cde.org.cn/news.do?method=viewInfoCommon&id=314275

“主要研究者” and “进行中” at CDE website (as of 12 Sep 2018)

	医師名	所属	癌種	試験数
4	石远凯	中国医学科学院肿瘤医院内科	固形癌, 肺癌, リンパ腫等	61
11	秦叔逵	解放军南京八一医院全军肿瘤中心	肝細胞癌等	44
12	徐兵河	中国医学科学院肿瘤医院内科	固形癌, 乳癌等	40
8	吴一龙	广东省人民医院肺癌研究所	肺癌等	38
9	沈琳	北京大学肿瘤医院消化肿瘤内科	固形癌, 胃癌(含接合部), 食道癌等	38
13	徐瑞华	中山大学肿瘤医院内科	固形癌, 大腸癌, 胃癌(含接合部)等	29
14	郭军	北京大学肿瘤医院 肾癌黑色素瘤内科	黒色腫, 尿路上皮癌, 腎細胞癌等	27
2	王建祥	中国医学科学院天津血液病 研究所白血病诊疗中心	白血病, 多発性骨髄腫等	15
6	江泽飞	军事医学研究院附属医院 乳腺肿瘤科	乳癌	14

CDE website: http://www.cde.org.cn/news.do?method=viewInfoCommon&id=314275

2018/8/8、CDEは海外上市済かつ中国で臨床上緊急ニーズのある新薬リスト(48品目)のパブコメを開始（8/18まで）

No.	Product Name (Active ingredient)	Company Name (MAH)	Place of First Approval	First approval date in EU, US or Japan	Therapeutic Area	Therapeutic target
1	Alectinib Hydrochloride	Chugai	Japan	2014/7/4	Tumor	ALK, RET
2	Pembrolizumab	MSD	US	2014/9/4	Tumor	PD-1
3	Olaparib	AstraZeneca	EU	2014/12/16	Tumor	PARP-1, PARP-2, PARP-3
11	Denosumab	Amgen Europe	EU	2010/5/26	Tumor	RANKL
14	Ponatinib	Ariad Pharma	US	2012/12/14	Tumor	EPH receptor, FGFR, Src, VEGFR, Kit, FLT-3, PDGFR, VEGFR, TIE2, RET
18	Palbociclib	PfizerInc	US	2015/2/3	Tumor	CDK4; CDK6
20	Enasidenib mesylate	Celgene	US	2017/8/1	Tumor	IDH2
23	Vismodegib	Genentech	US	2012/1/30	Tumor	SMO
33	Dinutuximab	United Therapeutics	US	2015/3/10	Tumor	GD2
34	Sonidegib	Novartis	US	2015/7/24	Tumor	SMO
35	Olaratumab	Lilly	US	2016/10/19	Tumor	-
38	Dinutuximab Beta	EUSA Pharma (UK)	EU	2017/5/8	Tumor	GD2

CDE website: http://www.cde.org.cn/news.do?method=viewInfoCommon&id=314651

中国における抗がん剤等開発環境の変遷

年	主な出来事(施行日等)
-2003	SDA設立(1998)； 輸入薬のP3 MRCT解禁(2002/12/1)； 当局組織改変SDA→SFDA(2003/4)； 中国にてICH-GCP施行(2003/9/1)
2006	Icotinib P1 IND承認
2007	現行医薬品登録管理弁法(SFDA局令第28号)施行(10/1)
2011	第12次5カ年計画(政府主導のバイオ医薬品産業育成支援,2011-2015)； Icotinib承認(11M)
2012	Pre-INDやPre-NDAを含むCDE communication meeting導入(7/16)
2013	当局組織改変SFDA→CFDA(3/22)； 低分子輸入薬でP(1-)2 MRCT実績(5月頃)； 輸入薬の三申請三承認制度適用開始(12/23)
2015	CFDA MRCT Guideline施行：国産薬のMRCT解禁か(3/1)； 国務院第44号令(8/18)：中国薬事規制改革開始
2016	第13次5カ年計画(政府主導のバイオ医薬品産業育成支援,2016-2020)； 抗がん剤等対象の優先審査制度開始(2/26)； 新薬の独自定義・化学薬品新分類施行(3/4)； MAH Pilot Program開始(6/6)
2017	Osimertinib承認(3月, 7M)； 中国ICH入り(6/1)； ワクチン製剤を除き輸入薬のMRCTをP1から解禁，輸入薬の三申請三承認制度を廃止(10/10)
2018	当局組織改変CFDA→CNDA(3/17)； 全ての輸入抗がん剤の関税を免除(5/1)； 中国ICH管理委員会入り(6/7)； Nivolumab承認(6月, 7M)； Pembrolizumab承認(7月, 5M)； 海外臨床試験データ受け入れの技術ガイドラインを制定(7/10)； IND審査制度を治験届制度に変更(7/27)； 海外上市済かつ中国で臨床上緊急ニーズのある新薬リスト(48品目)のパブコメ(8/8-18)； 当局の英語名称がNMPAに変更(9/1)； 中国にてICH-E17施行予定(12月)

中国における抗がん剤開発の今（まとめ）

1. 中国のかつての巨大ジェネリック企業は、低分子だけでなくバイオ医薬品も手がける新薬メーカーに変身している。豊富な資金力を背景に人材や抗がん剤パイプラインを充実させている。
2. 中国には、人材、抗がん剤パイプライン(低分子+Immuno-oncology+α) を豊富に持ち、それら複数治験薬の多癌種、多レジメンのP1～P3試験を中国・米国・グローバルで一斉に一気に押し進めることのできる資金力を有するバイオベンチャーが多く存在する。
3. 中国政府は、中国をバイオ医薬強国、世界の研究機関の中心にするべく、バイオ医薬品産業への重点支援を行っている。
4. 中国政府は、国内の医薬品産業育成ばかりでなく、世界同時開発の最先端の輸入抗がん剤の中国での治験実施ならびに中国への上市を優遇している。
5. 中国は米国に次ぐ世界第2位の医薬品市場を有する。ジェネリックの比重は依然として高いものの、高額抗がん剤の支払い能力も見込まれている。
6. CMOを用いたMAH制度導入、中国国産薬に対するMRCT解禁、輸入薬に対するP1 stageからのMRCT解禁、治験届制度導入によるIND審査期間の劇的短縮、優先審査制度導入等によるNDA審査期間の劇的短縮など種々の規制緩和により、中国内外の製薬企業・バイオベンチャーにとって、中国での抗がん剤開発・上市の重要性は近年急上昇している。
7. 中国で国家を代表するようなKOLs, key investigatorsには、国内外から抗がん剤治験が押し寄せ、かつてないほどの治験競合状況となっている。

Acknowledgments

- R&D-based Pharmaceutical Association Committee (RDPAC)
- RDPAC Regulatory Affairs/Intelligence Working Groups
- China Center for Food and Drug International Exchange (CCFDIE)
- Pharmaceuticals and Medical Devices Agency (PMDA)
- Japan Pharmaceutical Manufacturers Association (JPMA)

THANK YOU

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