Evaluation of nanotechnology-based medicines

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The views expressed in this presentation are those of the presenter and do not necessarily reflect the official views of Pharmaceuticals and Medical Devices Agency.

Outline

1. 1st International Workshop on Nanomedicines 2010
2. Review experiences of NDAs for nanotechnology-based medicines
3. Nanomedicine Initiative Project
4. Summary and Future perspectives

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1st International Workshop on Nanomedicines 2010 Summary Report

21 October 2010 EMA/538503/2010
Human Medicines Development and Evaluation

Program Committee:

EU Commission, EMA, MHLW/PMDA,US FDA

The workshop focused on key features of nanomedicines and the emerging scientific knowledge in the field. The objective of the workshop was to explore the science of nanomedicines and to share experience at an international level, in order to be able to anticipate future needs.

http://www.nihs.go.jp/drug/section4/nanomedicine%20workshop%20summary%20report.pdf

1st International Workshop on Nanomedicines 2010 Session Topics

- Keynote lecture
- Session 1: Special aspects of nanomedicines - Development, Manufacturing & Characterisation
- Session 2: Special aspects of nanomedicines – Non-Clinical Assessment
- Session 3: Nanomedicines on the market and in clinical development
- Session 4: Emerging nanomedicines
- Session 5: Nanomedicines and the application of Risk Management Principles
- Session 6: International outlook for Nanomedicines

http://www.nihs.go.jp/drug/section4/nanomedicine%20workshop%20summary%20report.pdf

Definition of Nanomedicines

Nanomedicine 8(5),849-56,2013

- "purpose designed", often using multiple components, and all have at least one dimension in the "nano-size range".
- Rationale for design
  - improved drug delivery（drug targeting ：organ-specific, cell-specific or subcellular targeting)
  - controlled and/or site-specific release
  - improved drug transport across biological barriers.
  - developed for external activation

    as carriers of combination therapy/imaging agents/vaccine delivery systems.
- Specific pathophysiological conditions

  trigger pharmacological activity

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Drug Delivery Systems : materials, technology, purpose “conventional/traditional” vs “nano-sized”

materials/technology	examples	main purpose
conventional surfactants (e.g. polysorbates)		solubilization extended/prolonged release
lipid (e.g. phospholipids, cholesterol)	microemulsion liposomes	
polymers	nanoparticles nanocapsules copolymers	long circulating targeting imaging
other materials		

Review experiences of NDAs for nanotechnology-based medicines in Japan: Examples of approved products

Classes	Brand name Red:Orhan/Priority review	Non-proprietary name (JAN) * Genetical Recombination	NDA category	Year Approved
Liposomes	DOXIL	Doxorubcn Hydrochloride	(4)(5)(6)	2007
	AmBisome	AmphotericinB	(5)(6)	2006
	Visudyne	Verteporfin	(1)	2003
Protein polymer conjugates	PEGASYS	Peginterferon Alfa-2a*	(1)	2003
	PEGINTRON	Peginterferon Alfa-2b*	(1)	2004
	SOMAVERT	Pegvisomant *	(1)	2007
	MIRCERA	Epoetin Beta Pegol*	(1)	2011
	(Neulasta)	Pegfilgrastim*	(1)	2014
	Cimzia	Certolizumab Pegol*	(1)	2012
Nanocrystals	EMEND	Aprepitant	(1)	2009
	XEPLION	Paliperidone Palmitate	(1)	2013
Nanoparticles	Abraxane	Paclitaxel	(5)(6)	2010

Review experiences of NDAs for nanotechnology-based medicines in Japan : Discussion points in review reports

- Characterization of quality attributes
- Release mechanism of API from the products
- Relationship between size and efficacy
- PK: concentrations in plasma and target site, organ distribution
- Toxicity: excipient, unexpected toxicity
- Comparisons with conventional (non-nano technology based) products : PK, toxicity

Review experiences of NDAs for nanotechnology-based medicines : Regulatory practice and general consensus

- Case by case evaluation and regulatory decision based on the NDA category,

  as a new molecular entity (1), new indication (4)/

  new dosage form (5) /new dose and administration (6)

- No specific review/regulation/guidance, but carefully considerations on rationale for design, materials and technologies.

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Recent regulatory activities regarding nanotechnology-based medicines in Japan

- MHLW/EMA collaborative work for the reflection paper on the development of block copolymer micelle medicinal products
- MHLW organized discussion group on nanomedicines (kicked-off in 2011)
- Open discussion/cooperation
  - MHLW regulators/NIHS researchers/PMDA reviewers
  - Academia/Industry/Regulatory bodies
  - International regulatory bodies

Project Team across Multi-offices in the PMDA

http://www.pmda.go.jp/kijunsakusei/nano.html

- In vitro companion Diagnostic Devices Project
- Pediatric and Orphan Drug Project
- QbD assessment Project
- Innovative Statistical Strategies for New Drug Development
- **Nanomedicine Initiative Project**
- Global Clinical Study Project
- Cardiovascular Risk Evaluation Project
- Omics Project

Nanomedicine Initiative Project -1/2

http://www.pmda.go.jp/kijunsakusei/nano.html

About this Project

Nanotechnology-based medicines are anticipating to improve the benefit-risk balance of drugs.
In this project, point to consider for regulatory requirements for nanomedicine development is discussed.

- When: June 2011
- Offices: New Drugs, Biologics, Regulatory Science, Standards/Guidelines Development, Review Management,
- Professionals: Quality, Pharmacology/Pharmacokinetics, Toxicology, Excipient

Nanomedicine Initiative Project -2/2

http://www.pmda.go.jp/kijunsakusei/nano.html

What we did

- Assisted to prepare “Joint MHLW/EMA reflection paper on the development of block copolymer micelle medicinal products”

Several block copolymer micelle medicinal products are now under clinical or non-clinical developmental phases. To facilitate more appropriate development of nanotechnology-based medicines, the draft reflection paper was made. The draft reflection paper discusses the general principles for assessing block copolymer micelle medicinal products in non-clinical and early clinical studies.

- Assisted MHLW to prepare two management guidance on Clinical Trial Notification contained the points to consider in the case of some nanotechnology-based medicines.

  PFSB/ELD Notification No.05314 and No. 05318, dated May 31, 2013

- Assisted review/consultation teams

Joint MHLW/EMA reflection paper on the development of block copolymer micelle medicinal products

薬食審査発 0110 第 1 号
平成 26 年 1 月 10 日

各都道府県衛生主管部（局）長　殿

厚生労働省医薬食品局審査管理課長
（　公　印　　省　略　）

ブロック共重合体ミセル医薬品の開発に関する厚生労働省／欧州医薬品庁の共同リフレクションペーパーの公表等について

ナノテクノロジーを製剤技術に応用し、標的部位への医薬品の選択的な送達や生体内安定性の向上などにより、副作用の低減及び有効性の向上を目指した革新的医薬品の開発が世界的規模で進んでおり、その一つとしてブロック共重合体ミセル医薬品の開発が進んでいます。

そのため、厚生労働省と欧州医薬品庁は共同で、当該医薬品のより適切な開発を推進し、患者への迅速な提供を図る観点から、①品質及び非臨床評価について配慮すべき事項、②初めてヒトに投与する試験に先だって確認しておくべき事項について、リフレクションペーパーとして、とりまとめたものを日欧同時に公表することとしました。

欧州医薬品庁が公表するリフレクションペーパーとは、特に新しい分野で経験が限られている領域やトピックスに関する技術の現状を整理し、開発者との間で共有化を図る目的で作成される文書を指しますが、本邦においては、本リフレクションペーパーを、ブロック共重合体ミセル医薬品を開発する際の検討方法の手引きとして利用していただくことを目的として公表することとしました。貴管下関係業者等に対し周知方願います。

加えて、現時点では、ブロック共重合体ミセル医薬品に関する知見の集積は十分ではなく、個別の医薬品の開発に当たっては、独立行政法人医薬品医療機器総合機構と相談しながら進めるよう、貴管下関係業者等に対し合わせて周知方願います。

Joint MHLW/EMA reflection paper on the development of block copolymer micelle medicinal products

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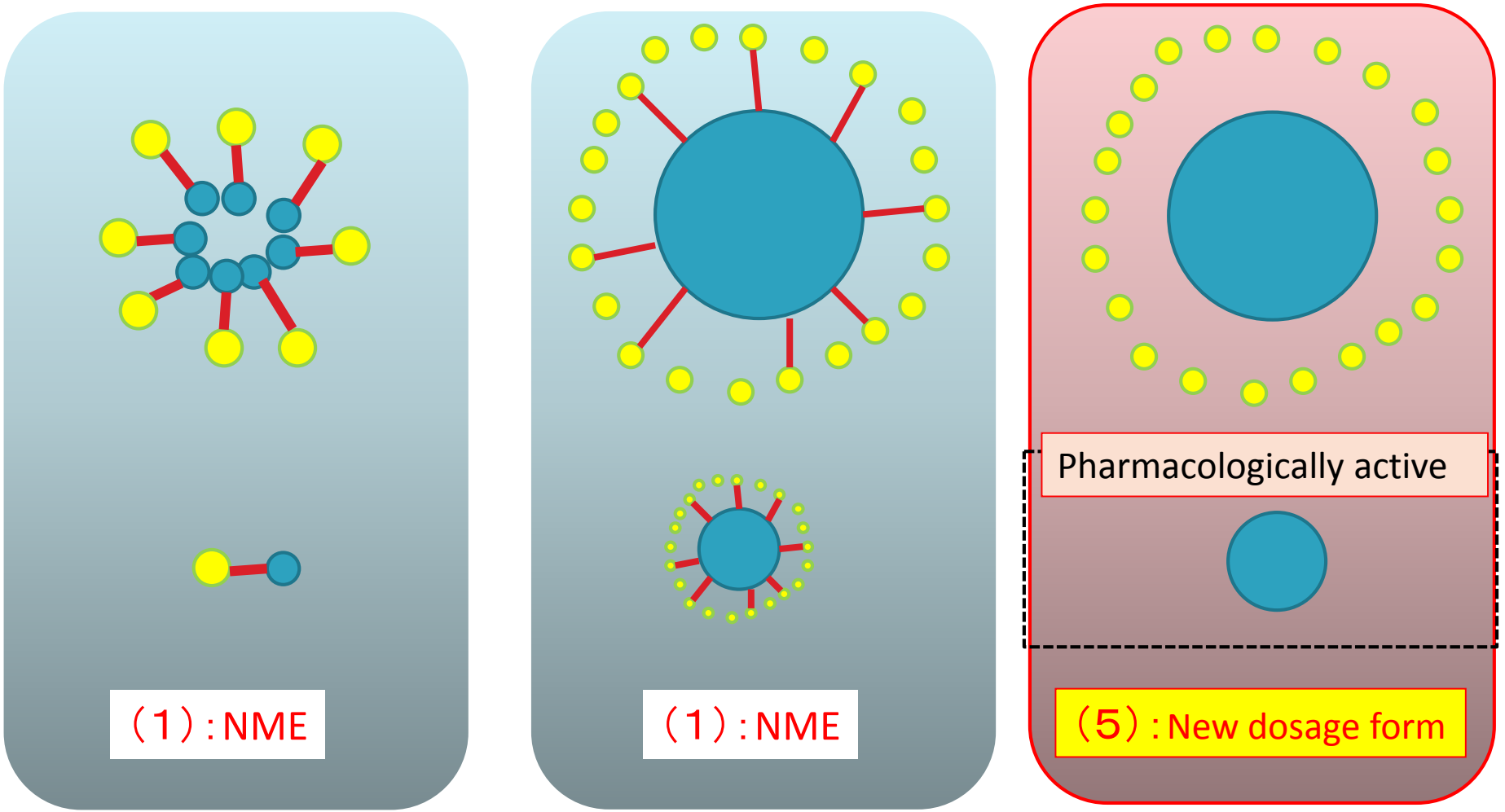
Management Guidance on Clinical Trial Notification

PFSB/ELD Notification No.05314 and No. 05318, dated May 31, 2013



Management Guidance on Clinical Trial Notification

PFSB/ELD Notification No.05314 and No. 05318, dated May 31, 2013

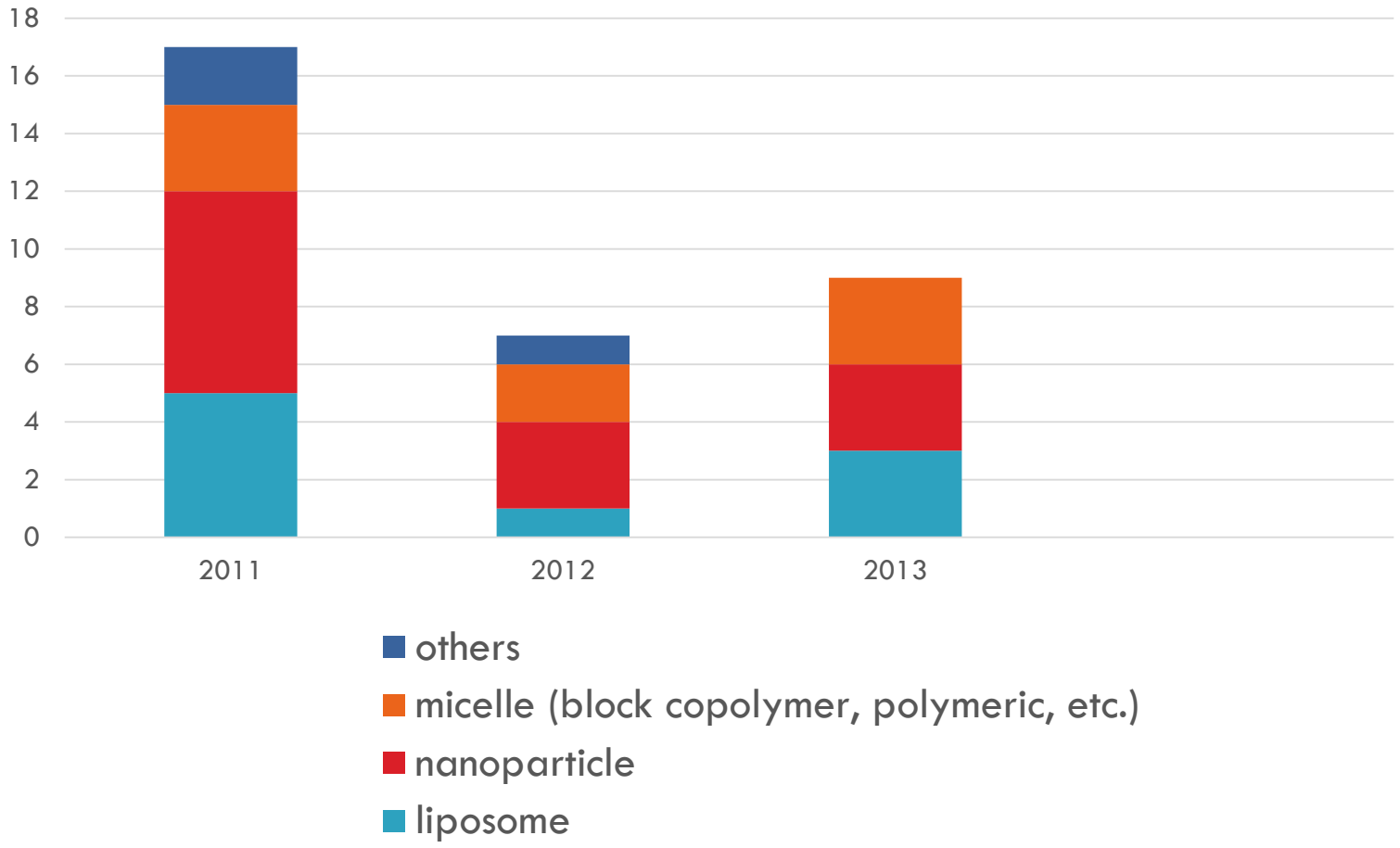
（７）届出時期については、届出の種類に応じ、原則として次によること。
① 治験計画届書（局長通知の別紙様式１）
ア 当該届出に係る治験の計画が３０日調査の対象となるものについては、治験薬提供者からの治験薬入手予定日又は当該治験の実施予定日の少なくとも３１日以上前に届け出

nanotechnology-based medicines

improved drug delivery (biodistribution, transport to target site) “purpose designed”

造販売 （外国製造
下「既承認医薬品等」
、例えばナノ技術を
応用すること等で徐放化等の
変更により用法等を異にすることを目的とした新たな剤形の
物のうち、有効成分を内包する等の製剤設計により有効成分の体内分布や標的部位への移行性が大きく異なると想定される薬物を用いた治験を届け出る場合には、上記アと同様に治験計画を届け出ること。

Consultations on nanotechnology-based medicine in PMDA



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Summary and Future perspectives -1/2

- Current situations
  - needs of discussion on nanomedicine-specific regulation
  - international regulatory cooperation (joint MHLW/ EMA reflection paper)
- Regulatory guides to assist nanomedicine development
  - 1st generation products (e.g. liposomes): guidance publication
  - Next-generation/novel products: discussion&reflection paper, especially to assist evaluation from pre-clinical to clinical stage (FIH and POC studies)

Summary and Future perspectives -2/2

- Points to consider for regulatory evaluation of nanotechnology-based new drug and nanosimilar GRPs for CMC, PK and toxicology reviewers
- Consultation/Review experiences for next-generation or novel products, nanomedicine/devices combination products and post marketing surveillance
- International collaboration on regulatory framework and guidances

Future Cooperation

- Cooperation in mutual understanding of guidance involving nanomedicines
- Information exchange on latest technology and regulatory evaluations on nanomedicines

Thank you for your attention!