Novartis Oncology

Enfoque en la calidad de los medicamentos y en la importancia de la farmacovigilancia

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Novartis es un líder mundial en oncología

Opera en 55 países con cerca de 7.000 empleados para oncología mundial

Ocho nuevos medicamentos que cambiaron la práctica de medicina en la última década con abordaje a necesidades médicas aun no cubiertas

Una amplia cartera de más de 28 nuevas entidades moleculares en desarrollo, apuntando las vías moleculares clave en la biología del cáncer

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El descubrimiento y desarrollo de fármacos lleva mucho tiempo

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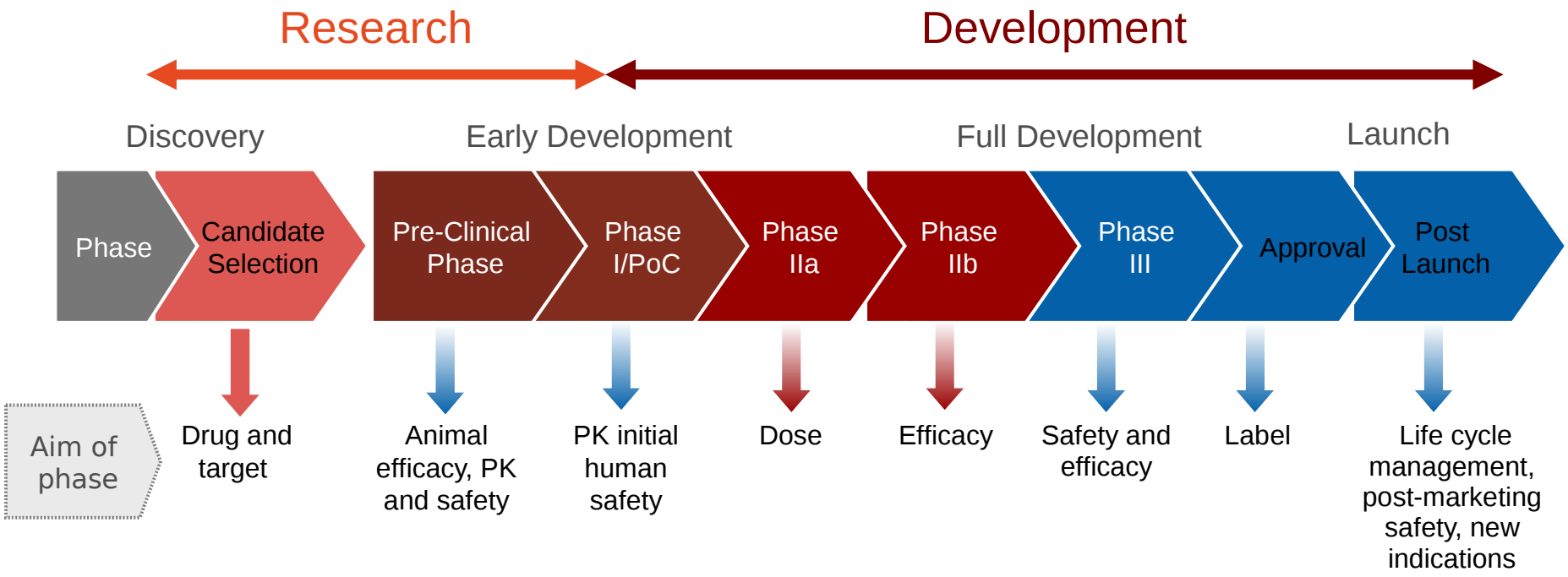
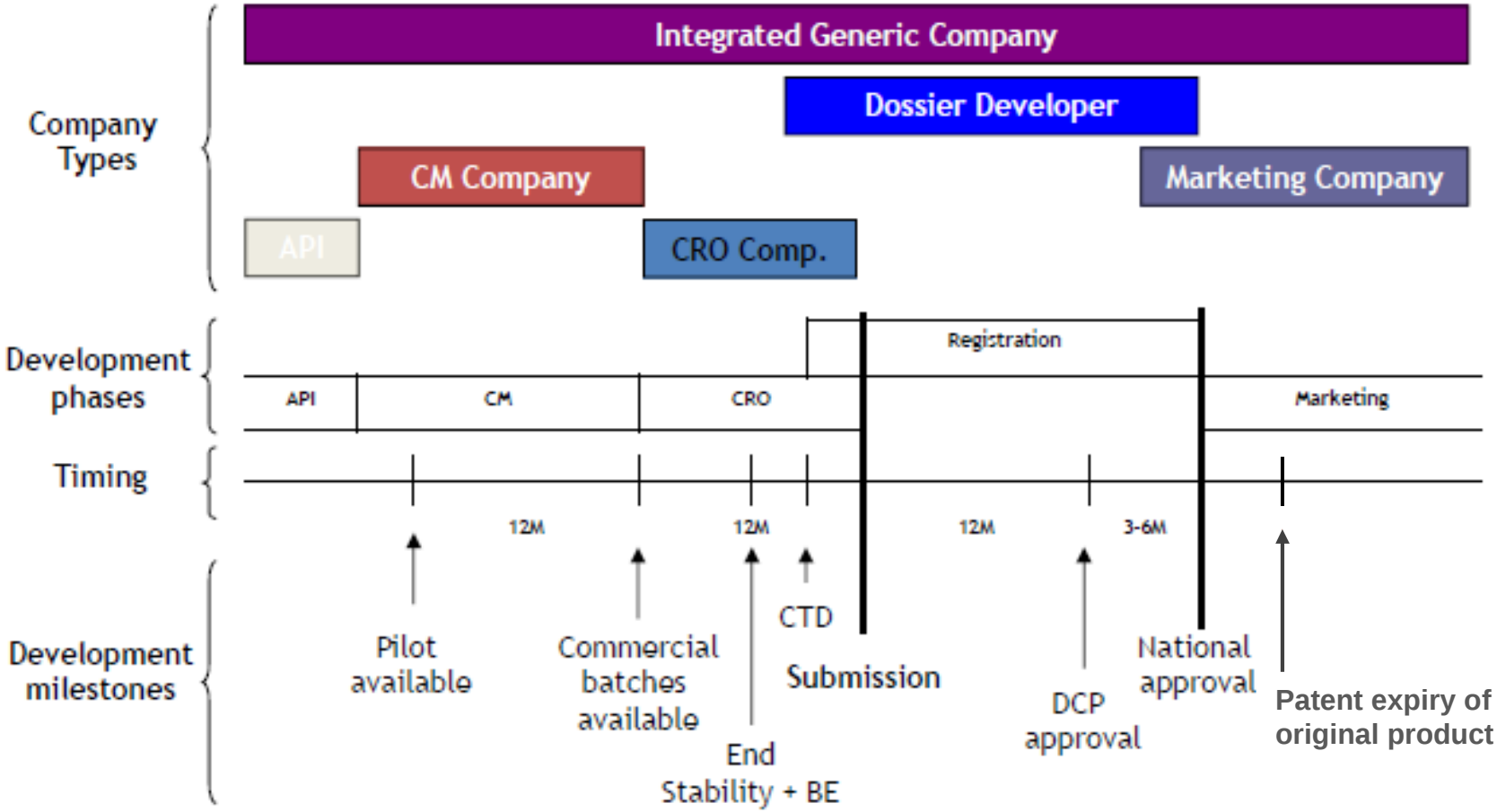
How new drugs can be developed



Adapted from USFDA Website: http://www.fda.gov/ForPatients/Approvals/Drugs/default.htm

Generics can be developed via different routes



- API= Active Pharmaceutical Ingredients
- CM: Contract Manufacturer

Source: TPR Group (Denmark), used with permission

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Los medicamentos de baja calidad no deben confundirse con los genéricos

Novartis se enfoca en la calidad

Esta presentación es acerca de productos de baja calidad,
no de productos farmacéuticos genéricos.

Novartis apoya los genéricos
y es la mayor empresa farmacéutica con
un importante negocio de genéricos en su portafolio: Sandoz

How drug quality is defined

World Health Organization's definition of quality:
"Quality assurance covers all activities aimed at ensuring that consumers and patients receive a product that meets established specifications and standards of quality, safety, and efficacy. It concerns both the quality of the products themselves and all the activities and services that may affect quality."[1]

Drug quality is affected by:	**Tablet/vial quality and labeling accuracy must be trusted by:**
• Standards of the product itself[1] • Manufacturing processes[1] • Distribution procedures[1]	• Physicians • Pharmacists • Patients

1. Torstensson D, Pugatch M. Keeping medicines safe–A study of the regulations guiding the approval of medicines in emerging markets. Stockholm Network 2010. At: http://www.stockholm-network.org/downloads/publications/Keeping_Medicines Safe_Final_Draft_2010. Accessed. August 15, 2013.

Why Quality Matters

Need to provide safe/effective drugs presents continuing global challenge for quality health care[1]

Challenges of healthcare globalization	• **PRO:** Free movement of healthcare products/services provides enormous benefits to patients • **CON:** This freedom of movement has also increased the prevalence of unsafe medicines[2]
Treatment/safety challenges	• Substandard drugs are becoming more common • Compromised products may provide no symptom relief or potentially be fatal[3]
Public health burden of substandard drugs	• Difficult to measure • How many deaths caused? • Time/money wasted on them?[4]
Increasing patient burden	• Increased outsourcing/international trading of medicines makes patients around the world more vulnerable[3]

1. Mechcatie E. IOM report addresses global problem of poor-quality drugs. *Intern Med News: digital network.* February 14, 2013.
2. Torstensson D, Pugatch M. Keeping medicines safe–A study of the regulations guiding the approval of medicines in emerging markets. Stockholm Network 2010.At: http://www.stockholm-network.org/downloads/publications/Keeping_Medicines_Safe_Final_Draft_2010. Accessed. August 15, 2013.
3. Attaran A, et al. How to achieve international action on falsified and substandard medicines. *BMJ*. 2012;345:e7381 doi:10.1136/bmj.e7381.
4. Countering the problem of falsified and substandard drugs. Report Brief. Institute of Medicine. February 2013

How quality is determined

International guidelines and standards

External Standards

- International Conference on Harmonization (ICH)[1]
- EMA[2] or FDA[3] requirements for drug approval, incl. bioequivalence and quality
- Pharmacopeias like EU, US, Japan etc.

Good Manufacturing Practice

- Use of scientific rationale and state-of-the-art technology
- Establishment of stringent specifications already during R&D stage
- Rigorous quality control and supply chain integrity
- Commitment to continual process improvements

EUROPEAN MEDICINES AGENCY
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[1] International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
[2] EMA = European Medicines Agency, Committee for Medicinal Products for Human Use
[3] FDA = US Food and Drug Administration, Code of Federal Regulations

How Reliable Are Your Generic Drugs From India? (2016)

Now that 88 percent of all prescriptions are dispensed as generic medications, the quality of such drugs is more important than ever. But the vast majority of them now come from abroad, where FDA oversight has historically been dismal.
http://www.peoplespharmacy.com/2016/02/15/how-reliable-are-your-generic-drugs-from-india/

Not all generic drugs are created equal: Why FDA, NIH and Congress need to protect Americans (2015)

Over the last couple years, there have been several major instances of popular generics failing to prove bioequivalent to the brand name they're based on.
http://www.foxnews.com/opinion/2015/03/19/not-all-generic-drugs-are-created-equal-why-fda-nih-and-congress-need-to.html

India Must Fix Its Drug Quality Problem (2014)

A working paper published through the U.S. National Bureau of Economic Research details the results of an extensive investigation into Indian pharmaceutical quality, examining nearly 1,500 India-made drug samples collected from 22 cities throughout Africa. The researchers found that fully 10 percent of the antibiotic and anti-tuberculosis samples contained insufficient levels of the key active ingredient. Patients are wasting their money purchasing pills that won't make them better. Worse still, low-quality pharmaceuticals can fuel the creation of drug-resistant disease.
http://www.forbes.com/sites/theapothecary/2014/09/17/india-must-fix-its-drug-quality-problem/#6fd17d405636

Are generics really the same as branded? (2013)

With an estimated 80% of active drug ingredients and 40% of finished medications coming from overseas — in some cases from manufacturing plants that the FDA has not yet inspected — quality can be significantly compromised.
http://fortune.com/2013/01/10/are-generics-really-the-same-as-branded-drugs/

Generic Drugs: Is Bioequivalence sufficient to ensure quality, efficacy and safety? (May 2015)

This article is focusing on the current debate that prescription of generic drugs is producing among patients and healthcare professionals. Following European Medicine Agency (EMA) recommendations, a number of generic medicines have recently been withdrawn from the market in Spain. The authorization for these generic drugs was primarily based on clinical studies conducted at GVK Biosciences in Hyderabad, India. **The EMA inspection of GVK revealed data manipulation of electrocardiograms during the development of some studies of generic medicines. These manipulations had taken place over a period of at least five years**. The article is also dealing with the consideration that bioavailability and bioequivalence studies receive as a cornerstone to approve generic drugs, and the discrepancies between the national regulatory agencies of medicines to implement guidelines of approval. Likewise, in the last few years, the rapid expansion of clinical trial activity regarding generic medicines and other drugs in emerging markets, is often leading to doubt on the integrity of the way trials were performed and on the reliability of data obtained from these studies.

Rev Enferm. Spanish
Carrillo Norte JA, Postigo Mota S.
http://www.ncbi.nlm.nih.gov/pubmed/26540896

US FDA Commissioner Califf calls on industry to tackle supply chain quality issues (June 9, 2016)

Risk algorithms and international agreements will help ensure imported API quality, says FDA Commissioner Robert Califf but industry must also take responsibility for its own supply chain. Califf was challenged as to how the **Agency will continue to try to ensure the safety of foreign-made APIs. Califf noted that there will be many more inspections in India and China.**

http://www.in-pharmatechnologist.com/Regulatory-Safety/FDA-Commissioner-calls-on-industry-to-tackle-supply-chain-quality

EMA highlights dozens of flaws at Dhanuka plant in India (May 25, 2016)

According to a Eudra GMDP report, Dhanuka Laboratories was found to have **32 shortfalls during a recent inspection.** Croatian authorities found the company to be in violation for its processes in producing cefixime, an API used to treat bacterial infections. The authorities found one critical deficiency--relating to a quality assurance system that was "weak"--and 7 major deficiencies, including shortfalls in quality assurance standards, facilities, documentation, material management, qualifications and lab controls. Dhanuka didn't have controls to assure that its batches were up to snuff, the regulators said, and contamination was possible due to the facility not meeting GMP requirements. Additionally, "core principles of the management of electronic documentation was found not considered (or disregarded)," according to the EudraGMDP report.

http://www.fiercepharma.com/manufacturing/ema-highlights-dozens-flaws-at-dhanuka-plant-india

Italian regulator slams simvastatin maker for GMP deviations (May 23, 2016)

Italian Medicines Agency said **APIs made** by Krebs **in an Indian facility pose a "critical risk" to public health.** IMA posted its concerns on the EudraGMP database. Inspectors identified 24 deviations from GMP, including major deviations in crystallization, finishing and quality control procedures.

http://www.in-pharmatechnologist.com/Ingredients/Italian-regulator-slams-simvastatin-maker-Krebs-for-GMP-deviations

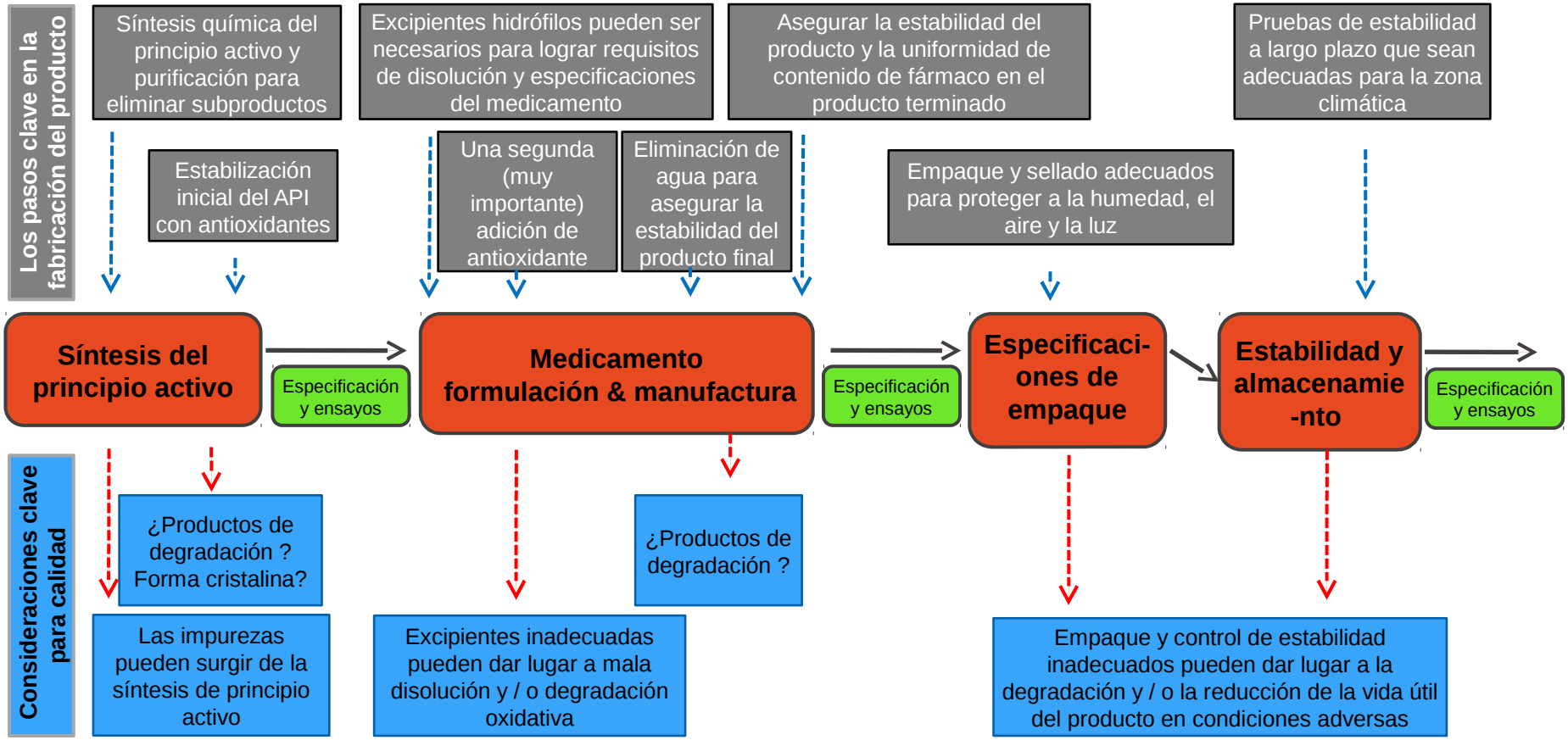
Why we need standardized quality guidelines

- **Patients** need reliable medicines with predictable results
- **Healthcare providers** expect outcomes that match those from clinical trials[1,2]
- **Governments** (and all payers) expect value from their healthcare spending[1,2]

1. Blier P. Q&A session: generic substitution for psychotropic drugs. 2009.
2. Desmarais JE, et al. Switching from brand-name to generic psychotropic medications: a literature review. CNS Neuroscience & Therapeutics. 2011;17:750-760.

Los pasos clave en la fabricación del Producto X

Identificados como críticos para la calidad del producto por su fabricante – manufactura del Hardware



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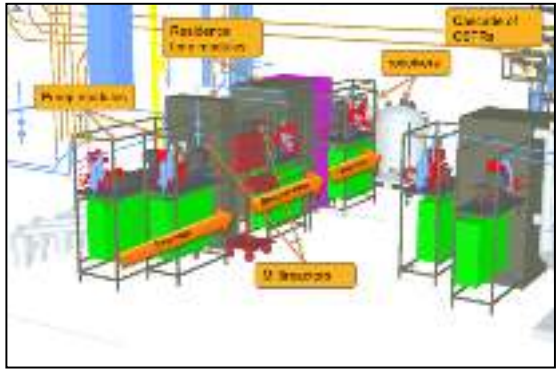
Innovations in clinical manufacturing

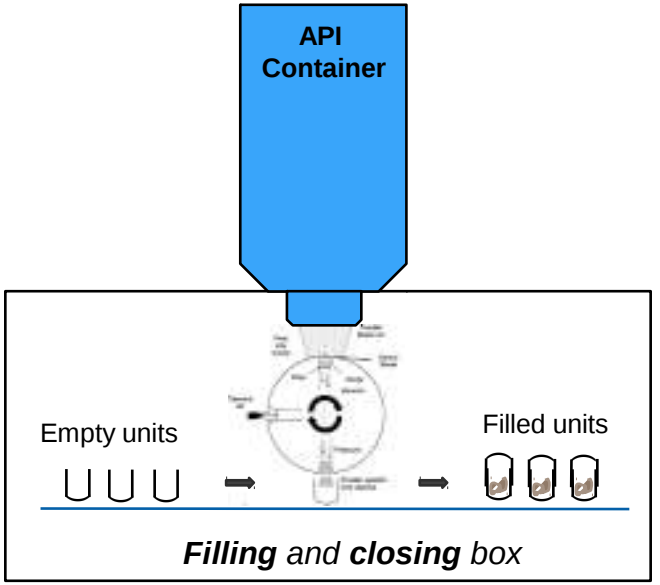
Taking manufacturing to the 21st century

Continuous manufacturing of API



The first ever multipurpose continuous pilot plant becomes fully operational in 2014

Direct capsule filling of API



- **Faster transition to clinical phases**
- **Increased asset effectiveness**
- **Improved, more reproducible quality**

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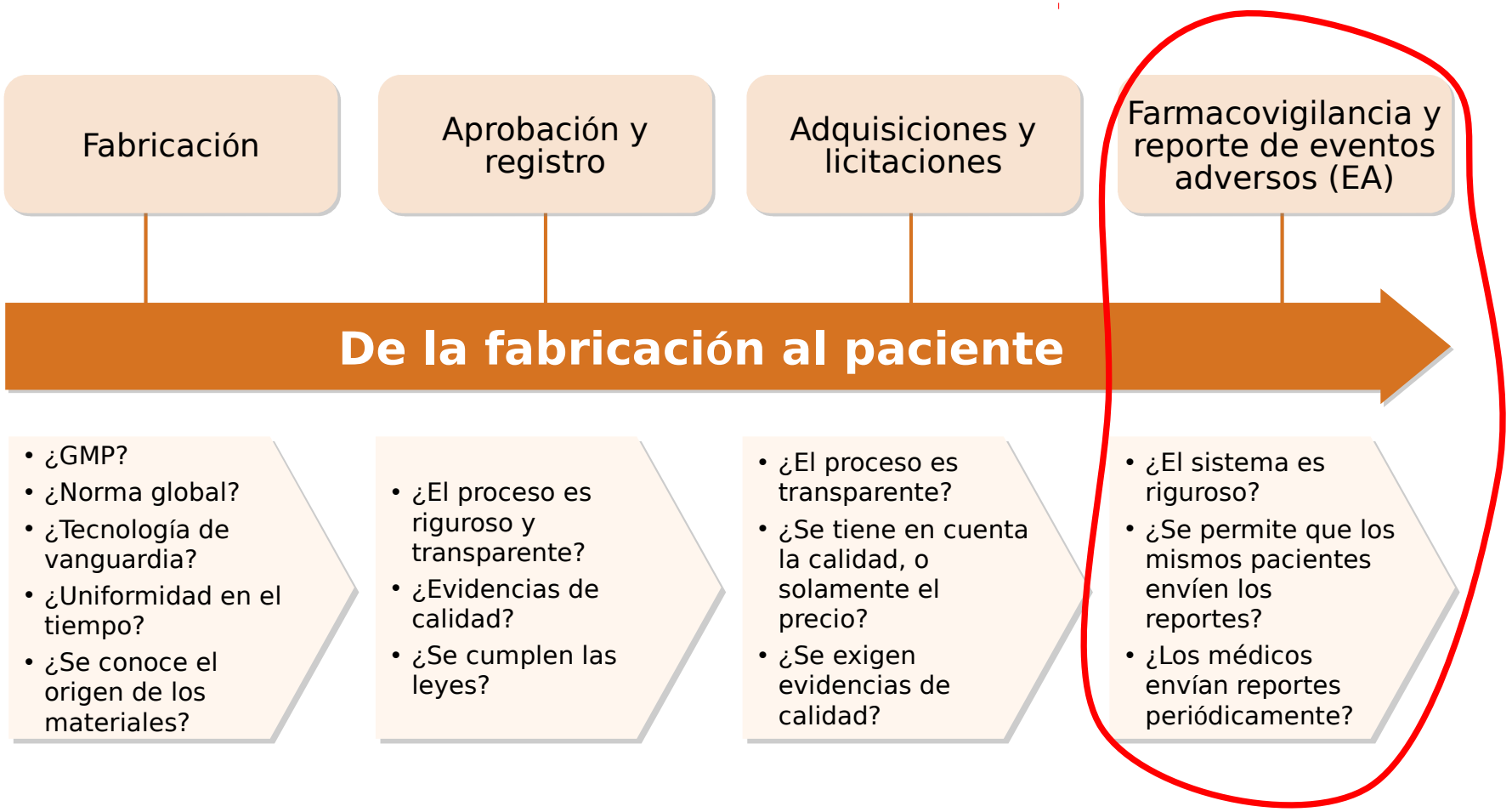
Todos podemos participar directamente proponiendo y apoyando la farmacovigilancia



1. Torstensson D, Pugatch M. Keeping medicines safe–A study of the regulations guiding the approval of medicines in emerging markets. Stockholm Network 2010. En: http://www.stockholm-network.org/downloads/publications Keeping_Medicines_Safe_Final_Draft_2010. Consultado el: 15 de agosto de 2013.

La OMS recomienda:

Establecer sistemas para la vigilancia continua de eventos adversos relacionados con medicamentos:

Es de vital importancia que existan mecanismos efectivos para el reporte de eventos adversos después de la aprobación regulatoria de un fármaco, ya que es virtualmente imposible suponer que, en la práctica clínica, la respuesta diaria de todos los pacientes a un producto farmacéutico será la misma que en un ensayo clínico controlado[1]

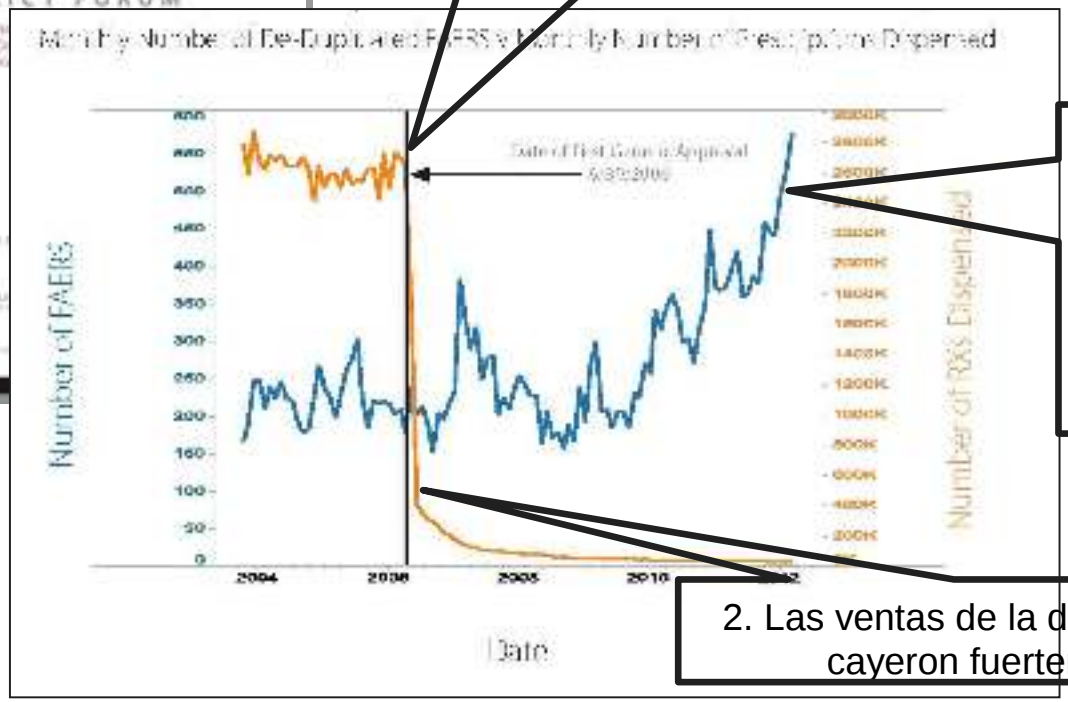
La vigilancia ayuda a las autoridades reguladoras a adoptar medidas más efectivas para:

- suspender la comercialización de un producto farmacéutico con algún problema
- promover retiros del mercado de los medicamentos en cuestión
- permitir que los sistemas regionales y nacionales pongan en alerta a los profesional de la salud y al público en general acerca de los problemas[1]

1. Torstensson D, Pugatch M. Keeping medicines safe–A study of the regulations guiding the approval of medicines in emerging markets. Stockholm Network 2010. En: http://www.stockholm-network.org/downloads/publications Keeping_Medicines_Safe_Final_Draft_2010. Consultado el: 15 de agosto de 2013.

Cuando los eventos adversos son atribuidos al medicamento equivocado , el sistema no puede identificar los problemas

1. Otras versiones del medicamento aparecieron en el mercado aquí



3. Sin embargo, los informes de eventos adversos o bien se mantuvieron o comenzaron a aumentar. Pero el sistema de reportes no pudo diferenciar entre las diferentes versiones del medicamento

2. Las ventas de la droga original cayeron fuertemente

Este estudio muestra que eventos adversos fueran atribuidos al producto original mismo después de la entrada de los genéricos. Eso porque los reportes no distinguieron que versión del medicamento fue utilizado

FDLI Biosimilar Naming: How Do Adverse Event Reporting Data Support the Need for Distinct Nonproprietary Names for Biosimilars? Vol 3 (6) March 2013

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¿Cómo podemos trabajar juntos para avanzar en el futuro de los pacientes con cáncer?

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¡Muchas gracias!
¿Preguntas o comentarios?

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