3 – Overview of Drug Development: regulator’s perspective

Presentation to APEC Preliminary Workshop on Review of Drug Development in Clinical Trials

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Disclaimer: the information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop.
Objectives

• Phases of clinical trials
• Life of drug as seen by the regulator
• Common drug targets and future directions
• Current and future challenges and drivers for the regulator
Phases of Clinical Trials

Phase I
- Initial safety & tolerability
- Determine safe dosage range
- PK / PD
- 20 – 80 subjects

Phase II
- Explore efficacy
- Dose response
- Continue evaluation of safety
- 100 – 300 subjects

Drug product life-cycle

Phase III
- Confirm efficacy
- Continue evaluation of safety
- Compare to commonly used treatments
- Collect information for safe use
- 1,000 – 5,000 subjects

Phase IV
- Post-market optimization
- Safety in the general population
- Patient population sample
Drug Molecule Life as Seen by Regulator

Exploring other applications

New disease indications
New route of administration
New population

Continuous monitoring and assessment of safety

Phase I  Phase II  Phase III  1st Regulatory approval  1st Generics

Small scale  Larger scale  Commercial scale  Impact of generics

Non-clinical testing

Years since patent first filed by innovator

Impact of generics
Larger scale
Commercial scale
1st Regulatory approval
Phase III
Phase II
Phase I
4 8 12 16 20 24
Dr. Paul Ehrlich coined the term “magic bullet” ~1900 and discovered Salvarsan® (arsphenamine), a treatment for syphilis.
Finding Drug Targets

- Discovery of DNA
- Development in molecular genetics techniques and other advanced research techniques
- Elucidation of signalling pathways associated with disease
- Study of targets *in vitro* & in animal models
- Target

1953

Today

Continuously ongoing
Targets for Drug Development

Unmet medical needs…

- Oncology - angiogenesis, cell signalling receptors and molecules in tumour growth
- Cardiovascular and metabolic diseases – type 2 diabetes, obesity, atherosclerosis/thrombosis
- CNS - Alzheimer’s Disease, Parkinson’s disease, affective disorders
- HIV / AIDS - novel targets in viral life cycle
- Infectious diseases - hepatitis B and C, influenza
- Asthma, COPD
- Autoimmune and inflammatory diseases - arthritis, psoriasis, inflammatory bowel disease, multiple sclerosis
Future Directions (1)

- Current approach in drug development is focused on targeting specific cell signalling pathways.
- Despite new targets such as receptor tyrosine kinases, tumour necrosis factor, cyclooxygenase-2, vascular endothelial growth factor, bcr-abl, proteasomes, immunomodulators, etc., still have ineffective therapies with serious side effects.
- 100’s of genes could be disrupted in different cancers and in other diseases.
- Multiple molecular players & signalling networks in disease.
- Need better understanding of drug targets and long-term safety outcomes.
Future Directions (2)

- Need to focus drug development on safety and efficacy
- Early detection of potential pitfalls using biomarkers, surrogate markers, imaging techniques, phase 0 trials
- Complexity of the mechanisms of disease such as oncogenesis may require targeting multiple targets in sequence or in parallel, for induction and maintenance of disease remission
- Complexity of the mechanisms of disease should drive future research to better understand the mechanisms and translate knowledge into clinical drug research
- Need to continue focus on developing products to address potential urgent public health needs (e.g., pandemic influenza)
Current and Future Challenges and Drivers

Regulation of Drug Development

- Aging population
- Regional issues
- ↑ Complexity of Innovations
- ↑ Public knowledge & pressure
- Globalization
- Biomarkers & Surrogate markers
- Adaptive CT designs
- Pharmaco-Genomics & Individualized therapy
- ↑ costs

Current and Future Challenges and Drivers
Multidisciplinary = ↑ collaboration

Regulatory modernization to keep pace with advances
## References

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<td>FDA’s Critical Path Initiative – Opportunities List</td>
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<td><a href="http://www.fda.gov/oc/initiatives/criticalpath/reports/opp_list.pdf">www.fda.gov/oc/initiatives/criticalpath/reports/opp_list.pdf</a></td>
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