API Outsourced Manufacturing in Italy: A Biopharma Company's Perspective

Forum Aschimfarma, October 18, 2016

Dr. Regan G. Shea
Senior Vice President, Chemical and Biologics Operations
Gilead Sciences, Inc., USA

GILEAD

Agenda

- Introduction to Gilead Sciences
- Our approach to outsourced manufacturing of APIs
- What we manufacture in Italy and benefits
- Special challenge of oncology medicines
- Regulatory harmonization progress and wish list
- Summary

Gilead Sciences Today

- A research-based biopharmaceutical company
  - Discover, develop, and commercialize medicines for areas of unmet medical need
  - Mission to advance the care of patients suffering from life-threatening diseases worldwide
- Formed in 1987, HQ in Foster City, California, USA
  - Estimated 2016 net product sales of $29.5B supported by 8746 employees
  - Established presence in more than 30 countries
- 23 marketed drugs; active R&D programs
- Therapeutic areas of focus:
  - HIV/AIDS, liver diseases, hematology and oncology, inflammatory and respiratory diseases, and cardiovascular conditions
- 13 successful acquisitions, growing company reach
- Committed to ensuring global access

Product Portfolio

HIV/AIDS

elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide

emtricitabine / rilpivirine / tenofovir alafenamide

elvitegravir / cobicistat / emtricitabine / tenofovir disoproxil fumarate

emtricitabine / rilpivirine / tenofovir disoproxil fumarate

efavirenz / emtricitabine / tenofovir disoproxil fumarate

emtricitabine / tenofovir alafenamide

emtricitabine / tenofovir disoproxil fumarate

emtricitabine

tenofovir disoproxil fumarate

HIV/AIDS

elvitegravir

cobicistat

Liver Diseases

sofosbuvir / velpatasvir
Chronic hepatitis C

ledipasvir / sofosbuvir
Chronic hepatitis C

sofosbuvir
Chronic hepatitis C

tenofovir disoproxil fumarate
Chronic hepatitis B

adefovir dipivoxil
Chronic hepatitis B

Hematology/Oncology

idelalisib
Chronic lymphocytic leukemia, follicular B-cell non-Hodgkin lymphoma and small lymphocytic lymphoma (US only)

Cardiovascular

ambrisentan
Pulmonary arterial hypertension

ranolazine
Chronic angina

regadenoson
Coronary vasodilatation

Inflammation/Respiratory

aztreonam
Cystic fibrosis

oseltamivir phosphate
Influenza A and B

Other

amphotericin B liposome
Fungal infections

pegaptanib sodium
Macular degeneration

Importance of Manufacturing Partners for Gilead

- We are primarily an R&D organization
  - Develop processes and scale up in-house
  - Internal commercial production limited to 1 API plant, 1 sterile vial plant, and 1 tablet plant
  - Rely on partnerships with CMOs
  - Our partners must be expert at production

- Manufacturing partners are strategic partners
  - Invest time and resources in our partners
  - Establish long-standing business relationships with core companies
  - Current CMOs are considered first for new opportunities

Rapid Development without Compromise on Quality

- We develop lifesaving products for the patients who need them, at full speed, without compromising on quality
- We choose API manufacturers willing to invest in staff, equipment, and facility upgrades that ensure quality
- Our success is assured by solely working with CMOs that, upon receiving audit or inspectional observations, agree to implement timely and robust corrective and preventative actions
- In Italy AIFA oversight and inspections, including an increased rate of unannounced inspections, help to assure continuous compliance with global GMP standards

Our API Manufacturing Supply Chain

- **Commercial pipeline**: 13 APIs (average 11 synthetic steps)
- **Development pipeline**: 22 APIs (average 16 synthetic steps)

- **API**: 13 CMOs
- **GMP and non-GMP precursors**: ~165 companies

- **A significant Italian contribution**
  - 6 CMOs operating 8 sites, including 4 making APIs
  - Approximately 20% of our API manufacturing
  - 6 Commercial APIs, 3 development APIs
  - 2 GMP intermediates, 25+ non-GMP custom chemicals

Value Proposition from Italian Manufacturing Partners

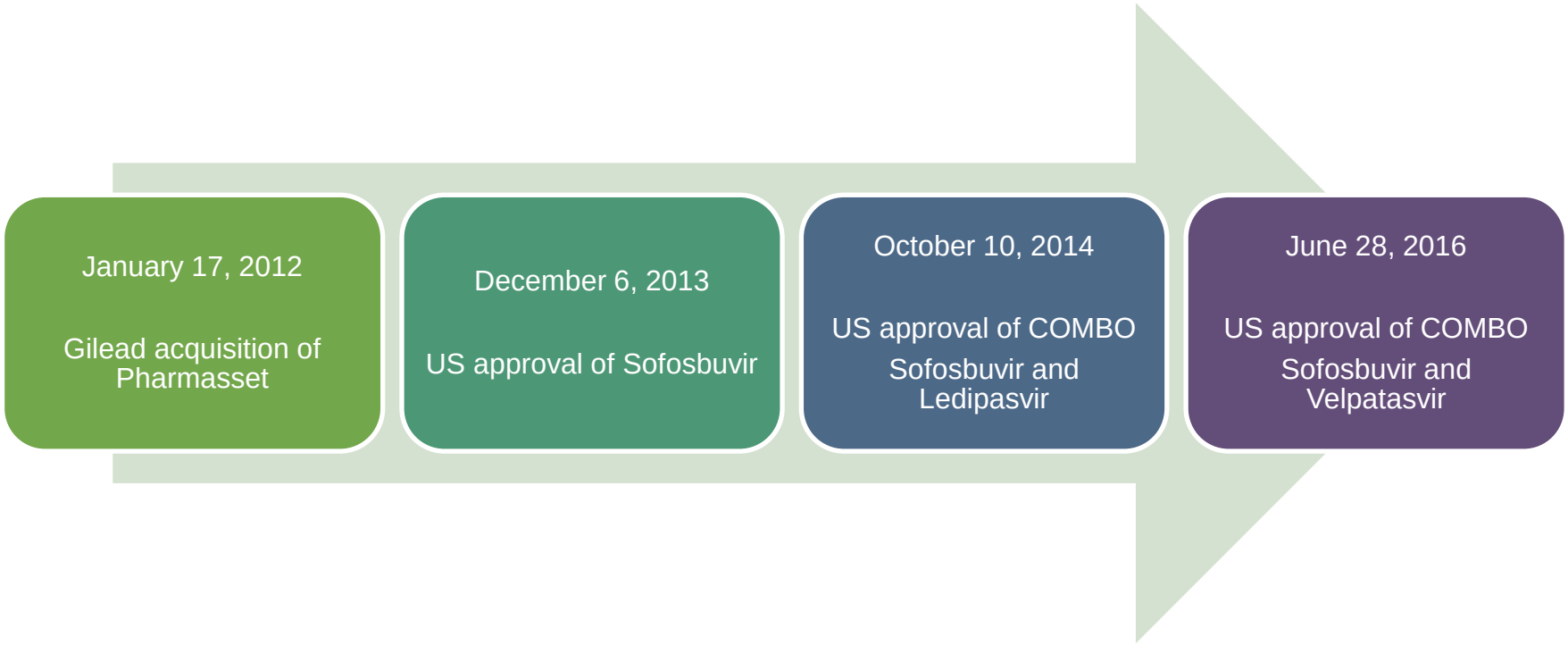
- Established organizations with a history of successful manufacturing
- Knowledgeable management having solid business relations with us
- Agility and flexibility to accommodate our requests
  - Bilingual batch records
  - Schedule adjustments per our needs, even on short notice
- Ongoing innovation to maintain competitive pricing
- Skilled process research & development and analytical resources
- Quality and compliance culture to continuously meet cGMP requirements and maintain good standing with regulators
- Adherence to delivery timelines

Italian Contribution to Gilead's Commercial APIs

API	Indication	API manufactured in Italy	RSM/GMP intermediates manufactured in Italy*
elvitegravir	HIV / AIDS	√	√
cobicistat	HIV / AIDS	√	√
sofosbuvir	Liver disease	√	√
ledipasvir	Liver disease		√
velpatasvir	Liver disease	√	√
ranolazine	Cardiovascular	√	
aztreonam	Inflammation	√	
idelalisib	Oncology		√*

*Materials made in overseas plants having Italian ownership

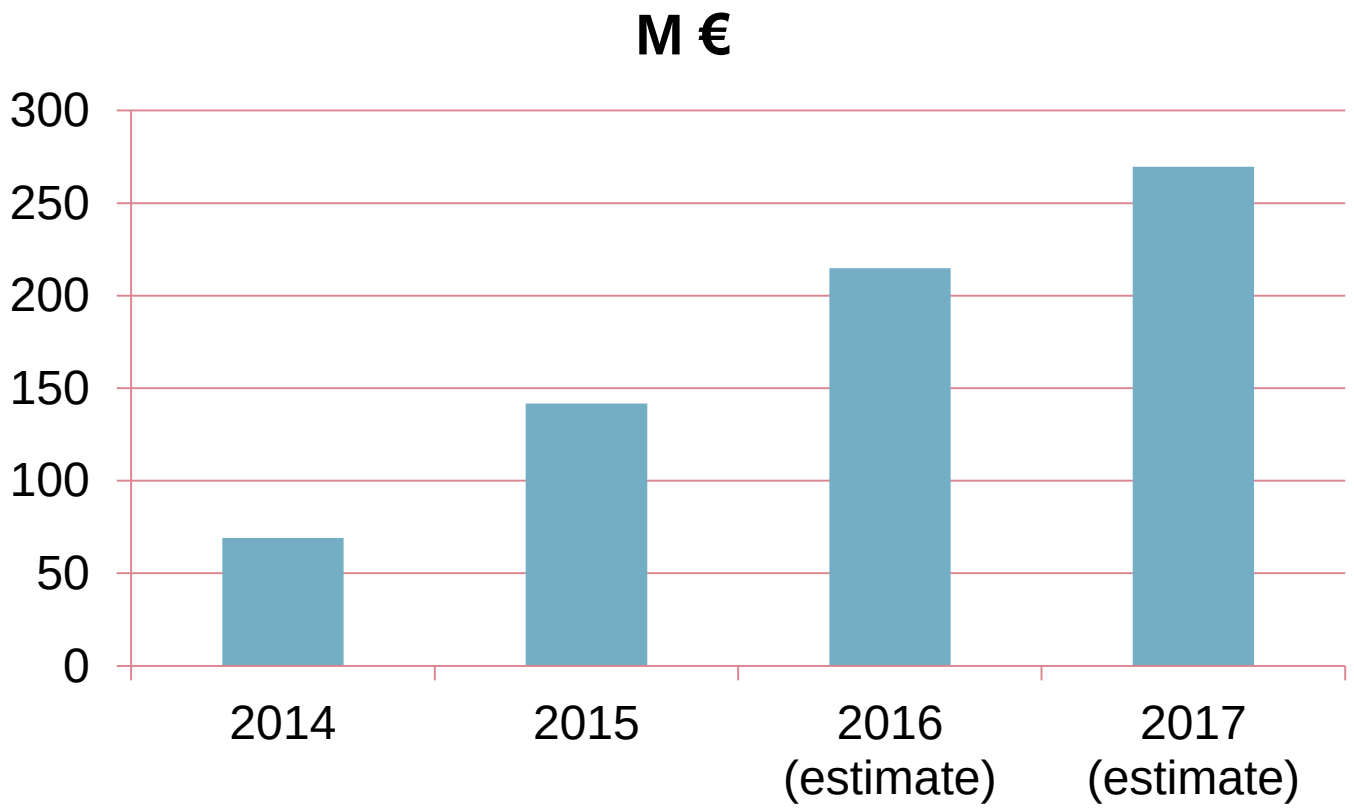
Italian Contribution to the Sofosbuvir-Based Hepatitis C Regimens



Italian manufacturers form the core of the supply chain for the HCV APIs: sofosbuvir, ledipasvir, and velpatasvir

The flexibility and accountability of Italian partners allowed Gilead to establish robust API supply chains supporting rapid product approvals and launches

Rapidly Increasing Manufacturing Spend in Italy



A First-in-Class PI3K Delta Inhibitor

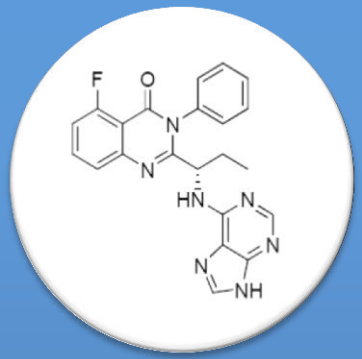
- Active ingredient is idelalisib
- Approved in the US for relapsed patients:
  - Chronic lymphocytic leukemia
  - Follicular B-cell non-Hodgkin lymphoma
  - Small lymphocytic lymphoma (US only)
- Launched during the 3rd quarter of 2014
- $41M in worldwide sales in 2Q 2016

Rapid Development of Idelalisib

Calistoga Acquisition

- Feb 22, 2011
- Phase 2 in progress

API Process Development and Validation



- API site selection
- Italian partners evaluated, not selected

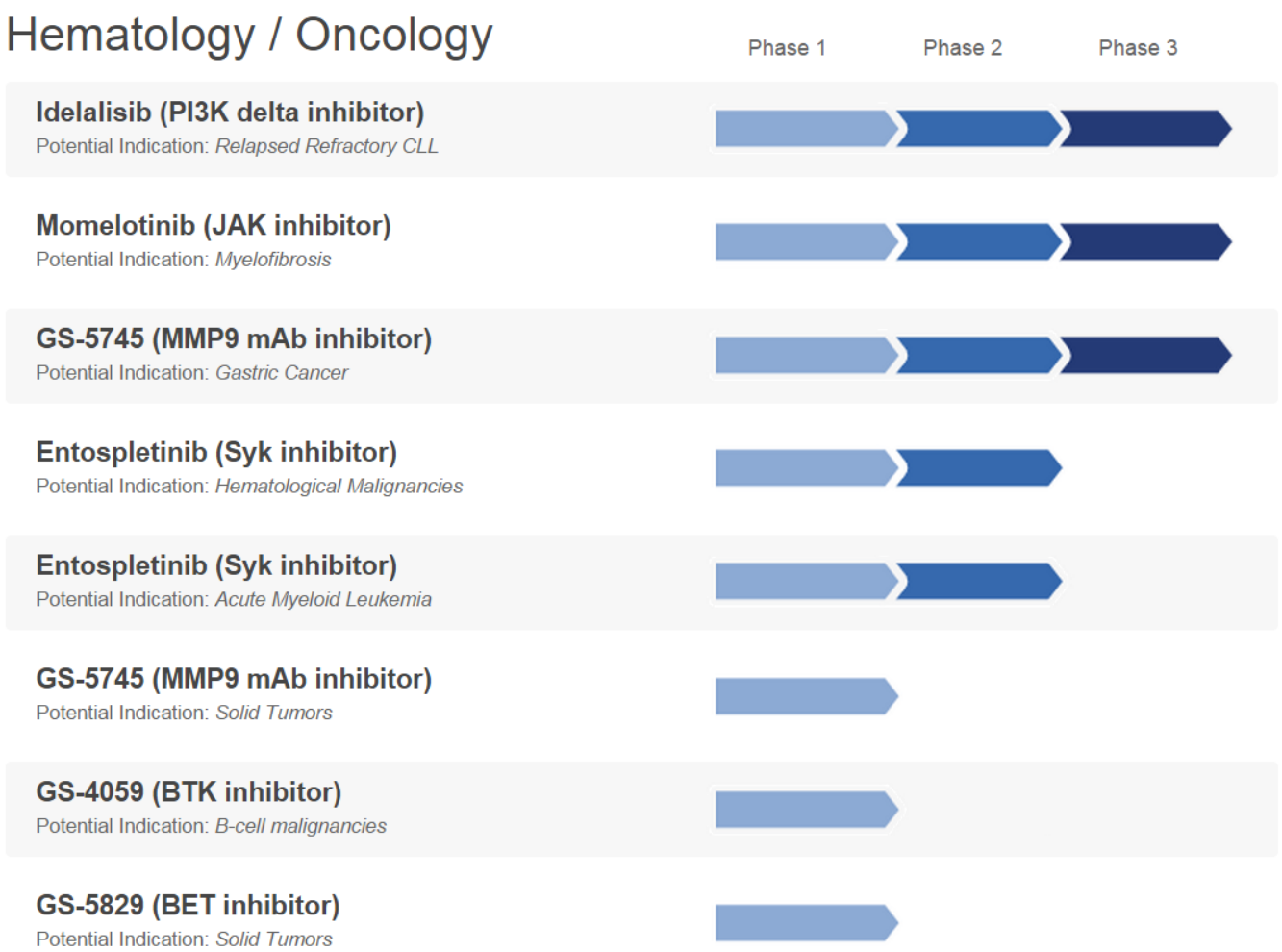
Registration

- US NDA
  - Submitted Sep 11, 2013
  - Approved July 23, 2014
- MAA
  - Submitted Oct 28, 2013
  - Approved Sep 18, 2014

Commercial Manufacturing

- Continued Process Verification and Improvement

Our Oncology Development Pipeline



Progress Towards Regulatory Harmonization

- Since November 2012, API supporting a Phase 1 study in an AIFA authorized facility can be manufactured with just a notification to AIFA
- AIFA recently expressed a positive opinion for extension of this expedited approach to APIs supporting Phase 2
- The extension of the notification to Phase 2 will remove a barrier to making API in Italy for late-phase clinical studies
  - We will be able to outsource more development stage projects to Italian sites without incurring study delays

What Remains on Our Wish List for Italy?

- Continue to keep the quality bar high
- Invest in science and technology to introduce improvements that contribute to globally competitive pricing
- Further harmonize the regulatory environment to help innovative companies move fast with Italian manufacturing partners
  - Ease restrictions on handling of new generation oncology APIs that are neither cytotoxic nor highly potent, taking into account a risk based approach
  - Implement an expedited notification procedure for API intended for Phase 2 studies
  - Adopt swift and certain response times for registration assessments, so that Italian CMOs may be routinely selected as launch sites

Summary

- Gilead has become a top 10 pharma company, conducting efficient development that delivers innovative medicines to treat life-threatening diseases worldwide
- Many of our core CMOs producing APIs and precursors are located in Italy, for reasons of quality, technical expertise, cost, capable ownership and management, and secure financing
- AIFA's high standards and active role help to ensure that Italian suppliers reliably make high quality APIs meeting global quality standards
- We look forward to continuing our investment in manufacturing in Italy; further evolution of the regulatory landscape could enable us do more work inside Italy to advance innovative therapies

Thank You

GILEAD