Elemental Impurities Program in Teva – Challenges and Expectations

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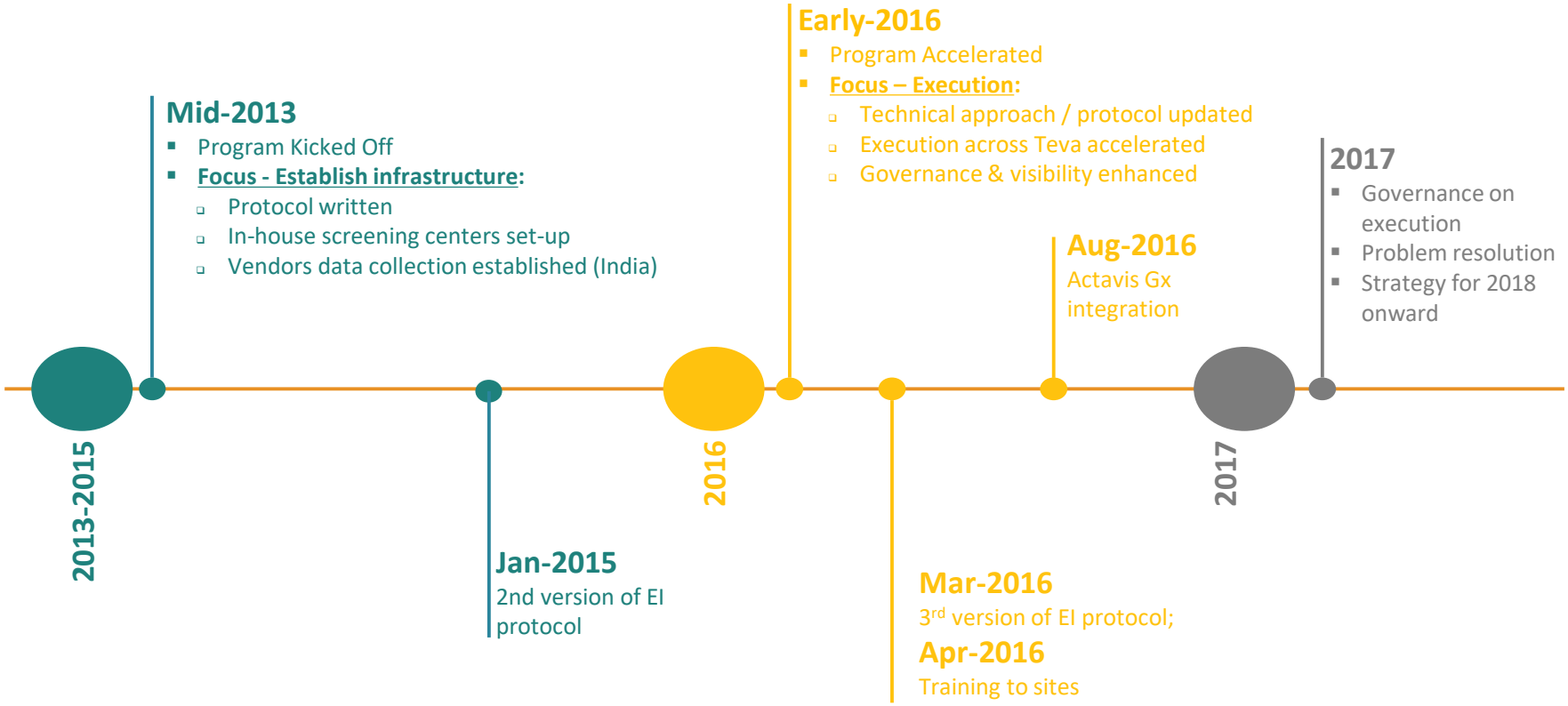
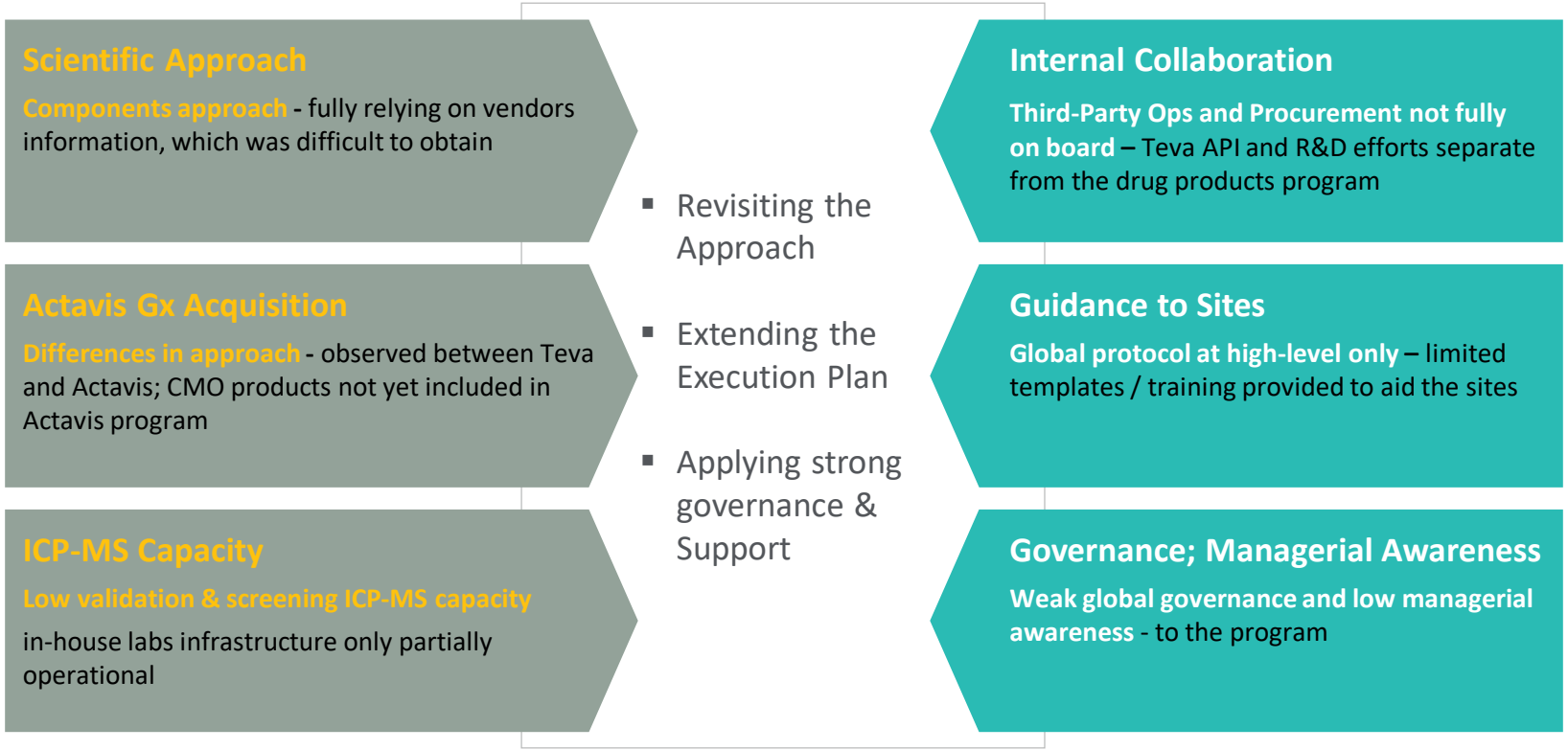
The numbers imply the magnitude and complexity of the program for Teva, No.1 Gx company in the world

> 40 Impacted Pharma Mfg. Plants	> 2500 Risk Assessments	> 900 Impacted CMOs and BD Partners
> 1500 Materials Vendors	> 90 US NDA/ANDA Submissions Since June 2016	> 2000 Drug Products Screening
11 ICP-MS Labs	> 450 Impacted APIs produced by Teva API division	> 40 EU Submissions (new files) Since June 2016

Program infrastructure was set-up starting in 2013, execution accelerated during 2016-2017



Challenges observed in early 2016 required “recalculation of route”



Revisiting the approach – Seeking for a practical approach, without compromising on compliance

Change	Benefits
Follow the "Drug Product Approach" rather than "Component Approach"; Collect components information for supporting & solidifying the Risk Assessment	✓ **More proactive and controllable approach** ✓ Assuming that all or most of our vendors will provide full data , on-time, on elemental impurities in their products - not realistic → May need to anyway screen the DP or components ✓ Amount of items to collect data on is not higher with the "drug product" approach - since in the "component approach" each unique combination of material/manufacturer/grade (catalog no.) requires separate data
3rd party products fully included in scope – CMOs expected to provide a risk assessment, BD partners (IP owners) a declaration of conformity	✓ **Comprehensive approach**
Full alignment of the scientific approach between legacy Actavis and Teva - no. of elements to screen, treating multiple strengths, etc.	✓ **Harmonized approach** ✓ **Compliant approach**

Extending the execution plan – Enabling on-time completion

Change	Benefits
Screening capacity expanded, to fit the required total number of screenings: 1. Utilize the already existing screening centers (Teva & Actavis) 2. Enhance capacity within the existing centers thru process efficiency 3. Source the missing capacity from external labs 4. Dynamic allocation of sites to labs, done globally	✓ **On time completion enabled -** by dynamically matching of capacity and demand ✓ **Quick availability of large capacity** ✓ **More flexible set-up** - Better fit with the life-cycle needs
Detailed training was provided to sites; Additional Q&A support session continue, and knowledge sharing between sites **Templates for Risk Assessments shared**	✓ **Sites enabled to execute effectively and efficiently** ✓ **Enhanced compliance**
Global team collecting data from vendors - mechanism was improved: vendors prioritization , SharePoint to sites etc.	✓ **Greater effectiveness of the components data collection**

Applying strong governance and support

Change	Benefits
Strong governance model applied: 1. Program defined one of a few “must have” programs in Quality 2. Steering Committee, led by Teva’s Head of Quality , meeting every month 3. Dedicated Project Manager 4. Focal Points at each site 5. Frequent work meetings at various forums 6. Monthly report	✓ **Management’s active involvement** ✓ **Visibility** ✓ **Effective execution**
Joint multi-disciplinary effort – collaboration of Global Quality with Sites, 3rd Party Ops, Teva API, Procurement, RA, R&D	✓ **Effective execution** ✓ **Good utilization of resources & expertise, Knowledge Sharing**
Risk Management – close monitoring, prioritization of products, analysis of market impact scenarios etc.	✓ **Contained Risks**

The readiness of Teva to January 1st 2018 is just around the corner

Data Collection from Vendors

Effort mostly extracted (partial responsiveness from vendors)

R&D Products

- Since June 2016 routine requests for compliance with Q3D for new registrations
- Teva has met the registration requirements, so far no real issues or delays to approvals

Teva API Risk Assessments

Mostly Completed

Drug Products Risk Assessments (CMOs)

The big majority provided Risk Assessment or committed to provide on time

Screening of Drug Products

Mostly Completed

Drug Products Risk Assessments (In-House)

Ongoing on high gear, still significant number to complete in Q4

Plans and expectations towards 2018

	Our Situation / Plans	Expectations

Science	▪ Our statistics so far (N>1000):
	  ▫ Only 1.4% of the products above threshold (30% of PDE)
	  ▫ None above limit (100% of PDE)
	▪ Teva's protocol provides guidance for revisiting the Risk Assessment
		▪ Q3D Assessment will replace the traditional Heavy Metal testing
		▪ For new regulations - authorities to provide as much as possible on-time and clear guidance, aligned between territories

Operations	▪ Sites will assume full responsibility for compliance, while global project is dismantled ▪ ICP-MS labs set-up is planned to be adjusted to a significantly lower demand	▪ Overall effort around Q3D in the "maintenance phase" is expected to be significantly lower, mostly derived from product/process changes ▪ Labwork will not have to be repeat in all cases, certainly not full validation
Compliance	▪ Potential scenarios of non-compliance were analyzed (e.g. Risk Assessment not completed, CAPA not completed) – Guidance being provided to sites and markets QP ▪ Large effort to complete readiness on-time; Risk Assessment to be documented in sites systems	▪ Q3D to be controlled through the regular internal systems, and as such would be an inspection point ▪ Authorities to seek balance between Q3D compliance and market needs

Acknowledgements

Many people from various professional disciplines are contributing to the Q3D program of Teva, among them:

- Michael Pesachovich
- Joseph De Vito
- Eyal Frost
- Demeitrius Sawickij
- Corinna Brandt
- Mathi Mathivanan
- Ronen Sharf
- Salimatou Dauphin
- Jay Rallapalli L
- Bat-Sheva Arama
- Yaron Shapiro
- Sharon Liberman
- Irena Poliakov
- Charmaine Gonsalves
- And many others…

Thank You!