Research and Technology – The New frontiers for pharmaceutical Industry – How can Italian CMOs support us to bring new products to the market?

Dr. Thomas Osswald, February 19th, 2017

Scope of Presentation

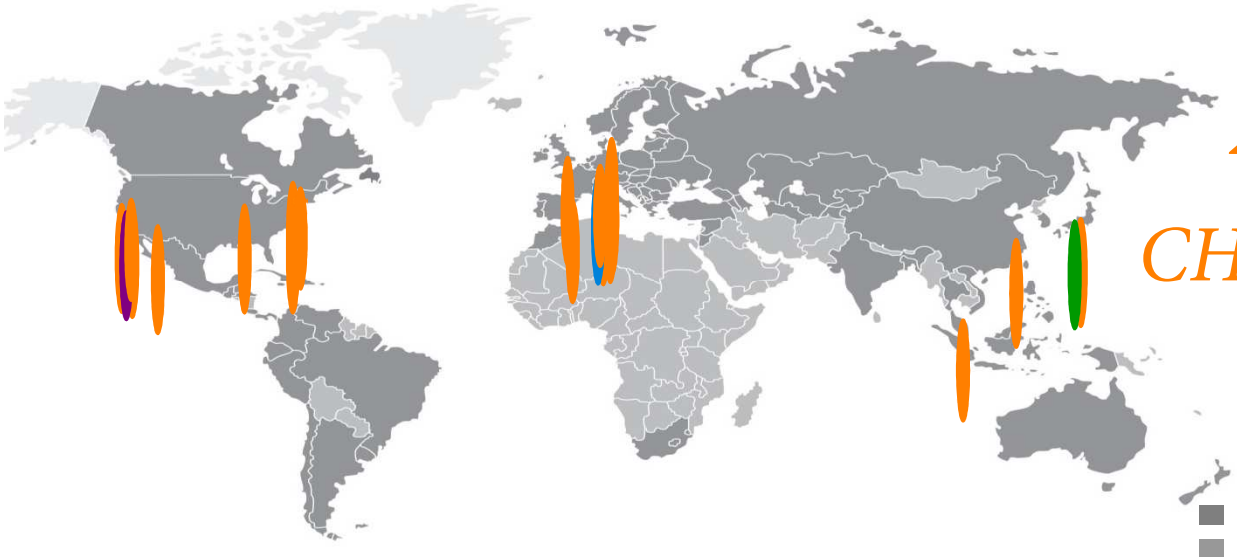
- **Who we are:** The Roche Organization (5 min)

- **What we need:** The changing landscape in Pharma and how (Italians) CMO can support us to bring new medicines to the market (15 min)

Roche

Basic facts at a glance – a global pioneer in pharmaceuticals

Among top 10 R&D investors worldwide (across industries)



94 052 employees* worldwide

22 major R&D sites in pharma and diagnostics worldwide

CHF 9.9 billion invested in innovative R&D

CHF 50.6 billion sales

Direct Roche commercial presence

Commercial distributors

Roche Group Headquarters in Basel, Switzerland

R&D sites in Pharma and Diagnostics

Genentech, R&D and commercial operations US

Chugai, R&D and commercial operations Japa

* *FTEs (full time equivalents)*

Roche

How we make a difference- Our contribution to healthcare

Oncology

Immunology

Infectious Diseases

Cardio-Metabolism

Neuroscience

Pulmonary

Ophthalmology

Scope of Presentation

- **Who we are:** The Roche Organization (5 min)

- **What we need:** The changing landscape in Pharma and how (Italians) CMOs can support us to meet our expectations.

CMC at Large Pharma

New Chemical Entities - Launches

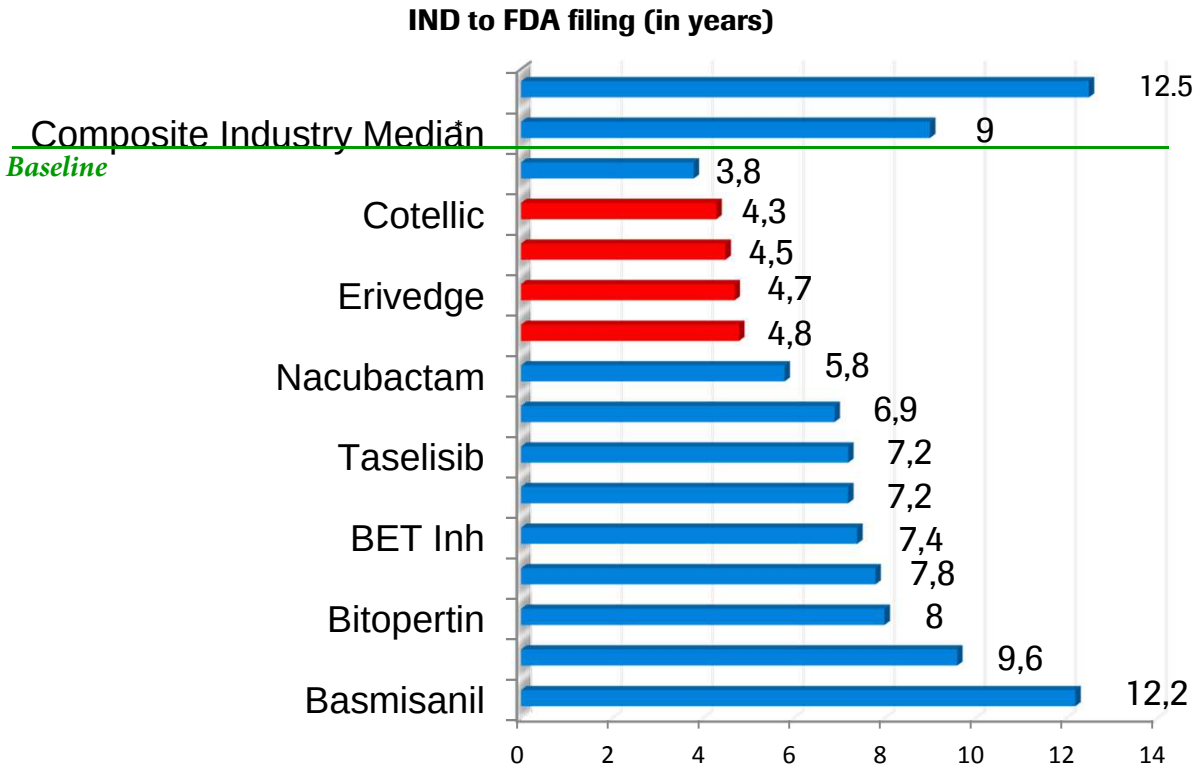
Theory

We have

- to be faster and to do more at the same time
- the products are more complex in its nature and
- In-house manufacturing capacity is decreasing at large Pharma

CMC at Large Pharma

Fast accelerations, de- and re-accelerations are new normal



Impact on us

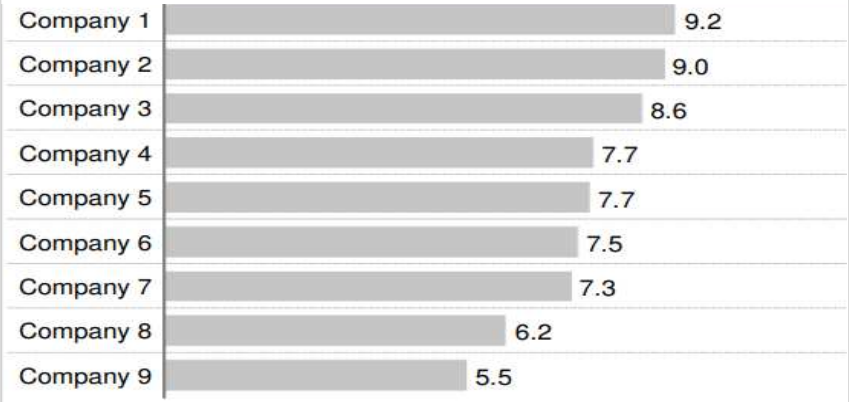
- Mindset shift – ramp up quickly, discipline to stop work temporarily
- Higher level of flexibility in work process and infrastructure
- This translate 1:1 to our partners – to you!

*Source: Industry cycle times from KMR Group, data from 2009-2013

CMC at Large Pharma
Portfolio with Greater Complexity

*Technical challenges due to increases in molecular complexity**

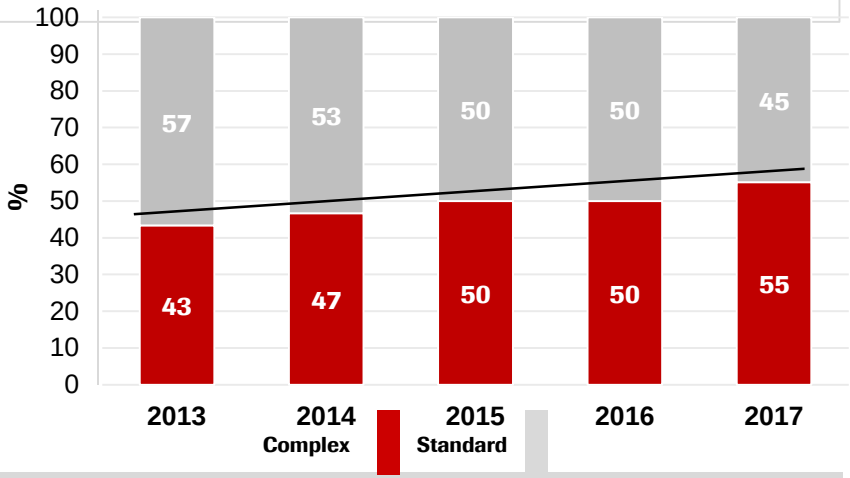
Average CMC portfolio complexity index of participants by company



Source: McKinsey Benchmark, November 2017

Peer group in McKinsey benchmark:
AZ, Bayer, Grunenthal, Lilly, Merck KGaA, Novartis, Roche, Sanofi, UCB. Complex projects start with a value of 6.

Complex vs Standard as % of portfolio



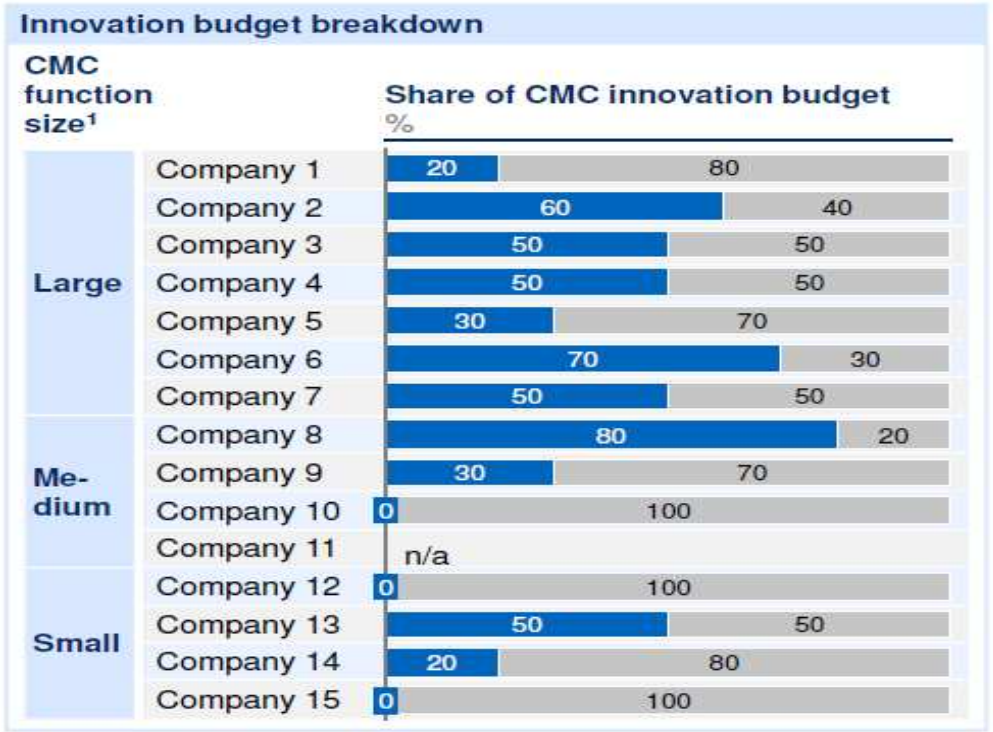
Significant increase in complexity in SM portfolio over past 5 years

** Molecular complexity criteria: Molecular properties (HHC), Complexity of DS synthesis & DP process, impurities, new modalities, formulation properties, device development, DS & DP stability*

CMC at Large Pharma

Where does Innovation come from?

1 CMC innovation budget – external spend: 80% of companies spending 50% or more of their CMC innovation budget externally

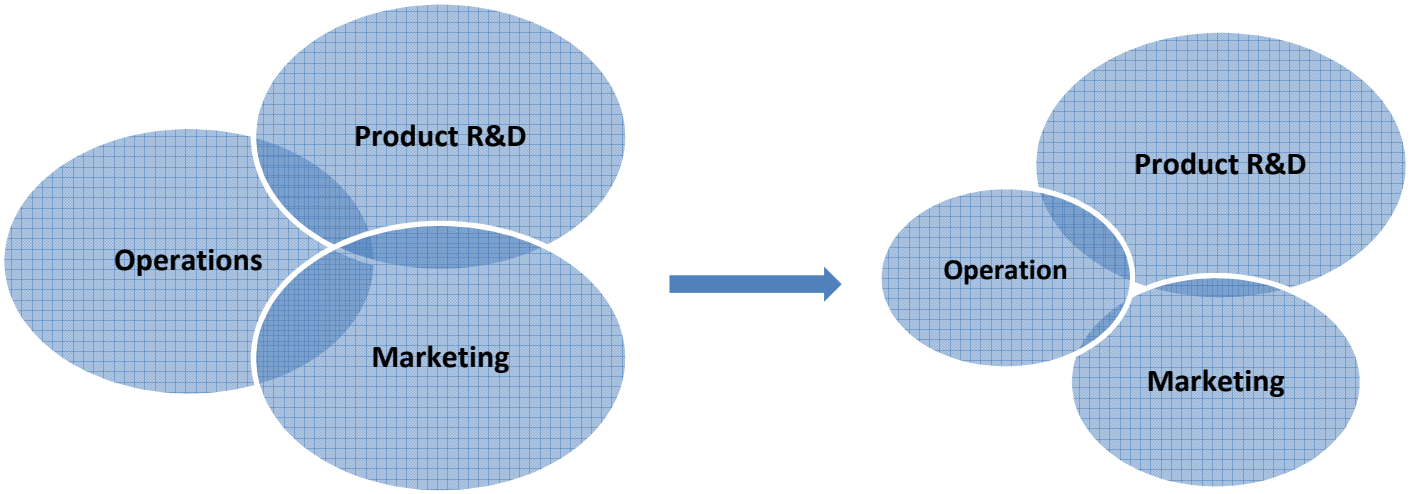


> *We expect disruptive innovation to come from outside*

> *Big innovation from start-ups and some innovative engineering companies*

CMC at Large Pharma

Where do we Produce the Molecules ?



- Constant decrease of internal manufacturing capabilities at large Pharma while focusing on Marketing and Product-development
- Focus on CMOs as source of Pharma's products (e.g. 54% of all DS – small molecules

Roche CMC

Pharma Technical Operations -19 plants at 16 sites

Not included on graph: well-established contract manufacturing organization (CMOs) network

Drug Substance:

- Small Molecules
- Biologics

Drug Product:

- Solid Dosage

CMC at Large Pharma

New Chemical Entities - Launches

Theory 2

We have

- ✓ to be faster and do more at the same time in a more unsteady environment
- ✓ the products are more complex in its nature and innovation is sought more and more outside Big Pharma
- ✓ In-house manufacturing capacity is decreasing at large Pharma and usually from second/third campaign onwards is done at CDMOs

Conclusion for our Partners - YOU ?

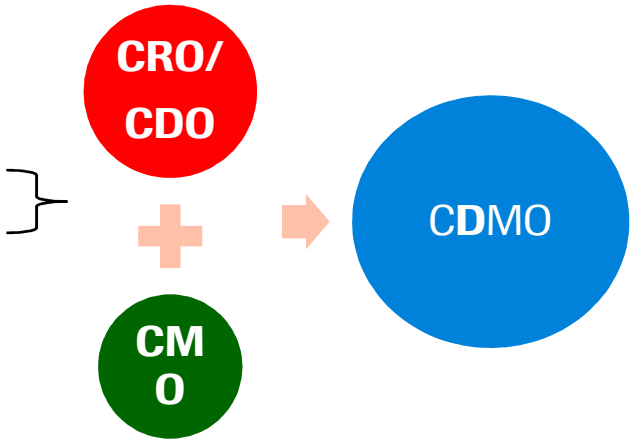
Outsourcing strategies

Our Ideal CMO - What do we mean with ideal?

Depending on the lifecycle of a product, the attributes of an ideal CMO are different:

An ideal CMO can fulfill all these requirements in order to avoid transfers, execute projects as needed with a high reliability.

	GMP	Cost/ kg	Agility	R&D	QC	QA	FDA/EMA
Preclinical	NA	++	+++	++	0	0	0
Phase I	+	+++	+++	+++	++	+	0
Phase II – III	+	++	+++	+++	+++	++	+
Launch	+++	++	++	0	+++	+++	+++
Established	+++	+	+	+	+++	+++	+++
End of Lifecycle - Divestment	+++	++	+	0	+++	+++	+++



Our Ideal CMO

Challenges in Today's Outsourcing

- Products are getting more complex
- Shortened development time line
- Increased in-/out-licensing deals in all phases of development leading to more product transfers (e.g. fit to existing portfolio)
- Tightened regulatory oversight
  - Increase number of FDA warning letters
  - RSM pushbacks making more steps under GMP necessary
- Diminishing internal resources to support outsourcing

When selecting CDMO partners, **economies of capabilities matter.**

- Putting the **D** in C**D**MO
- Quality culture- No spot on Quality and SHE
- Global regulatory experience
- Focus on various components
  - Regulatory starting materials
  - Advanced intermediates (GMP) and API
  - Services

Our Ideal CMO

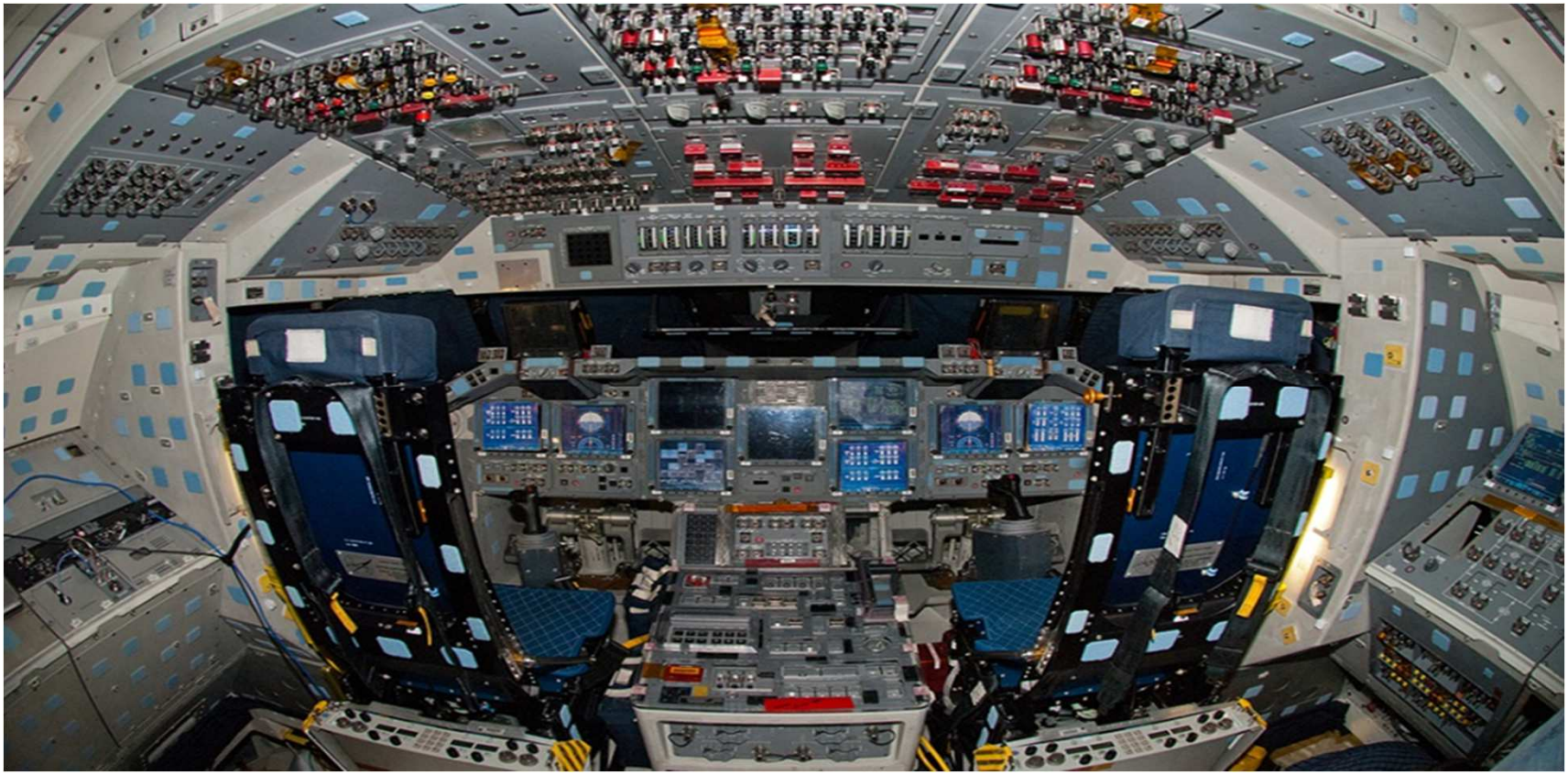
Some Key Considerations when selecting a CMO

R&D

- Critical mass on R&D (e.g. in Europe investments follow projects, in Asia the other way round leading to higher flexibility on the customer site)
  - An experienced team and not 2-3 chemists
  - An experienced team in Analytical development and QC, highly skilled in analytical method development and validation.
  - Key analytical equipment on site (e.g. LC-MS , ICP-MS, NMR)
  - Be fast, have latest regulatory requirements embraced
- R&D culture to develop the best process with appropriate robustness, yields and volume factors. Focus on manufacturability and innovation.
  - Experience in late stage development and process validation
  - Experience in design of experiments/understanding of NORs and PARs, knowledge of change control principles
- Good project-management across disciplines
- Fair and reasonable IP arrangement with full FTO for customer

Our Ideal CMO

Some Key Considerations when selecting a CMO – Cooperation



Our Ideal CMO

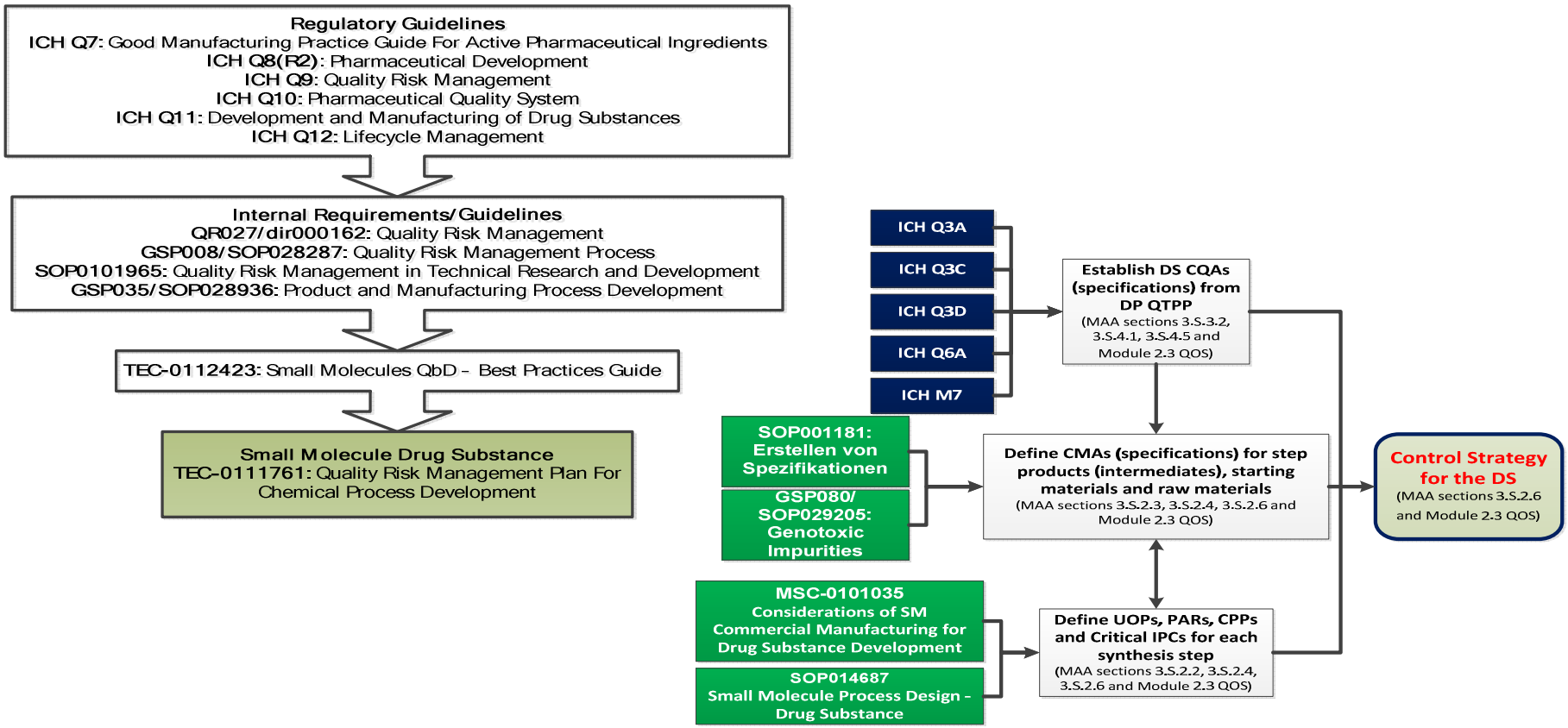
Some Key Considerations when selecting a CMO

Compliance in SHE /Quality and Experience in Regulatory ·

- Experience in regulatory filings of INDs, NDAs and MAAs
  - Ability to generate data which can be used for filing purposes
  - Ability to present data in reports, overviews in a concise and conclusive manner . Ability to scrutinize data for plausibility and context
  - Ability to provide rapid responses to regulatory questions and objections
- Fulfilling national and international SHE regulations and be a leader in this by
  - Establishment of a risk based decision culture
  - Fostering a high safety culture (e.g. technical risk management, process safety culture, BCP, …)
  - Appropriate Containment technolgies
- Satisfying compliance record and audit history with
  - Major HAs as AIFA, FDA, EMEA and JPN
  - No spot on burning topics (e.g. data integrity, CSV, supplier qualification, CAPA, ADE based cleaning concept, not following procedures, change control)
  - Experience in pre-approval inspections (PAI)
  - Modern Q system based on latest regulatory requirements (e.g. PPQ, control strategy)

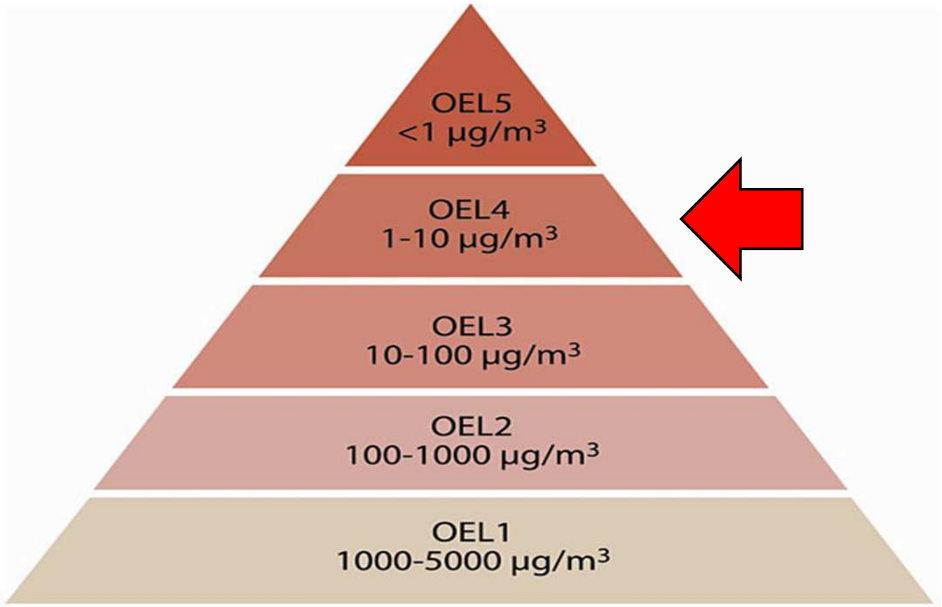
Our Ideal CMO

Excursus: Compliance as Key Success Factor



Our Ideal CMO

Excursus: Containment Technologies - A Nice to Have or a Must ?

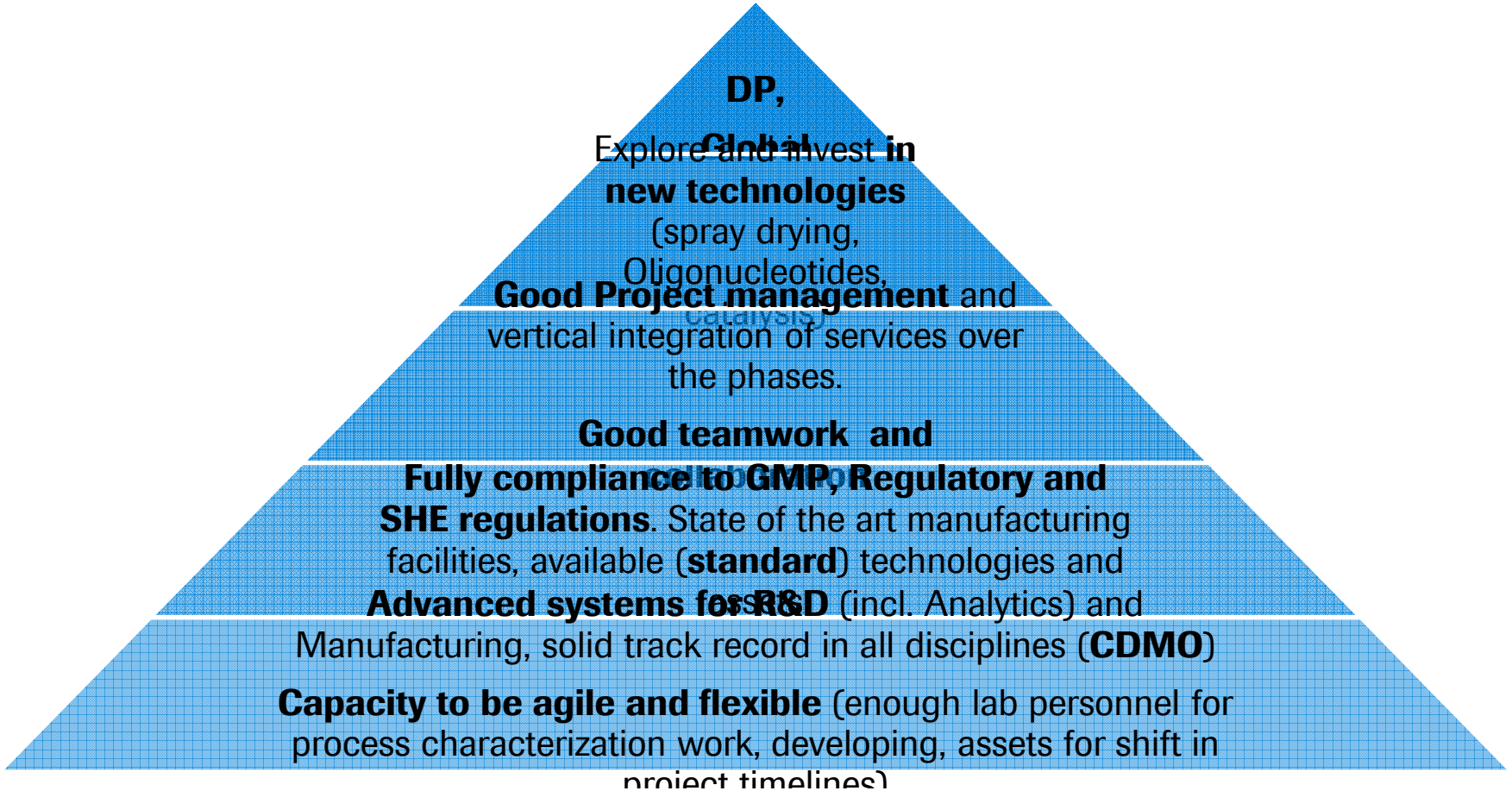


- Targeted research delivers more potent compounds; Oncology products due to its nature often belonging to potent compounds.
- In early phases, potency not clear; CMO has to have to have the capabilities to produce standard compounds (**OEL4, default category**) while using technical containment measures. In the later phase, classifications are more robust as more data becomes available
- Cleaning and handling concept should

KEY: Having appropriate containment technologies is a MUST to remain in and to have Business !

Final Words

My Pyramid of needs to CMOs



Final Words

How is Italy doing compared to a global level in the DS small molecule CDMO landscape

- Many family owned business giving long term perspective to the the business with swift decision making.
    - Investment level (also in emerging technologies) is significant and supportive of Pharma needs. Appreciated by customers
- Significant history in manufacturing and key strenght of Italian CMO business. High reliability in manufacturing area and other disciplines
    - Consolidation of manufacturing landscape is ongoing with site dis-investments, closure and revamping of sites. Chance is to develop an above average position in SHE, Quality and asset structure
- Many Italian companies now moving into the C**D**MO field but needs to invest in R&D (capacity, methodologies) to meet requests for agility and flexibility of customers and changed needs in regulatory environment

Doing now what patients need next

Our Ideal CMO

Some Key Considerations when selecting a CMO

Plant facilities for validation and commercial production

- Special process requirements are addressed with right equipment (not the other way round)
- Good IPC support and working on a 24/7 model.
- Facility has the right containment vs requirement for the product.

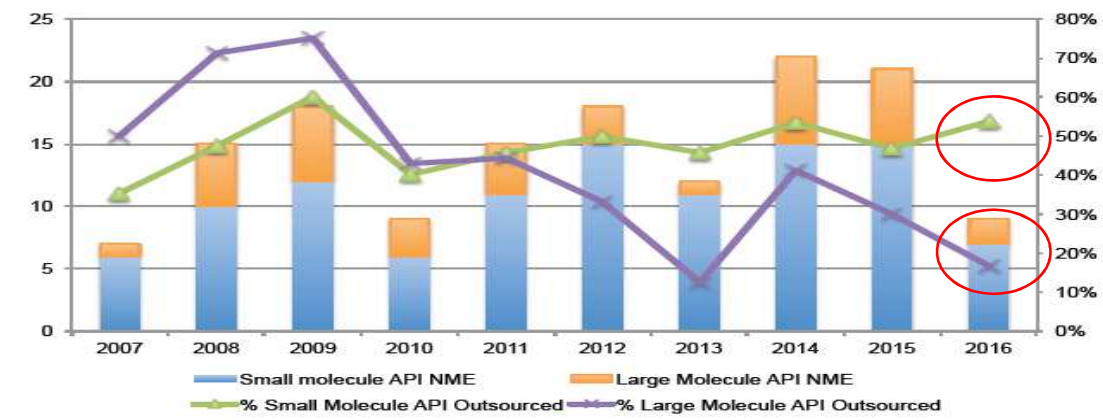
Commercial Expectations

- Competitive pricing
- Culture of implementation of manufacturing efficiencies & cost improvement for repeat business in the commercial scale. Also taking account raw materials.
- Robust, transparent and sustainable sourcing approach
- Array of manufacturing scales to cover demand fluctuations and various technologies
- Willingness to present and share innovation
- Maintain highest SHE and Quality standards

CMC at Large Pharma

Global Pharma Outsourcing Propensity 2007-2016

Figure 23 Outsourced NME API Manufacture 2007-2016



Source: PharmSource Analysis of FDA data

- Outsourcing of small molecule API manufacturing averaged 48% in the last decade, rising to 54 % in 2016.
- By contrast, only 18% of large molecules were outsourced during 2007-2016.
- NCEs are in the focus of the industry as they usually deliver higher margins than Generics.
- Focus of big Pharma is on launch and initial production.

Risk Assessment Tool for Regulatory Starting Materials

Regulatory Starting Materials

Written By Dr Will Watson on 18th July 2017. Process Chemisty Articles

SCIENTIFIC UPDATE
We've got chemistry

There have been a number of papers on the subject of how to specify regulatory starting materials, with a bench marking exercise carried out by the IQ Consortium[1]. Now a sub-group has published a risk assessment tool to evaluate potential regulatory starting materials[2],

a score is built up by counting:

A. The number of bond forming steps to the API.
B. Number of isolated steps to the API
C. % w/w of the API
D. Number of stereogenic centres
E. Number of substituted aryls or double bonds
F. Number of rings
G. Impurity carry over to the API
H. Instability

An overall score is built up using the following equation:

Risk score = 4/A + 8/B + (C x 0.6) + D + E + F + G + H

if the score is <8 the risk is considered low. A score of 8-10 carries a medium risk, and a score of >10 indicates a high risk.

1. M.M. Faul, W.F. Kriesman, M. Smulkowski, S. Pfeiffer , and C.A. Busacca, *Org. Process. Res. Dev.*, **2014**, *18*, 587-593.
2. L. Wigman, R.S. Oestrich, S. Hildbrand, H. Iwamura, F. Gosselin, W. Göhring, F. Schwarb, and J.-P. Crochard, *American Pharmaceutical Review*, A New Risk Assessment Tool for Regulatory Starting Material Evaluation, posted online on March 17, **2017**.

http://www.americanpharmaceuticalreview.com/Featured-Articles/335213-A-New-Risk-Assessment-Tool-for-Regulatory-Starting-Material-Evaluation/

NEWSLETTER
Issue 61, July 17

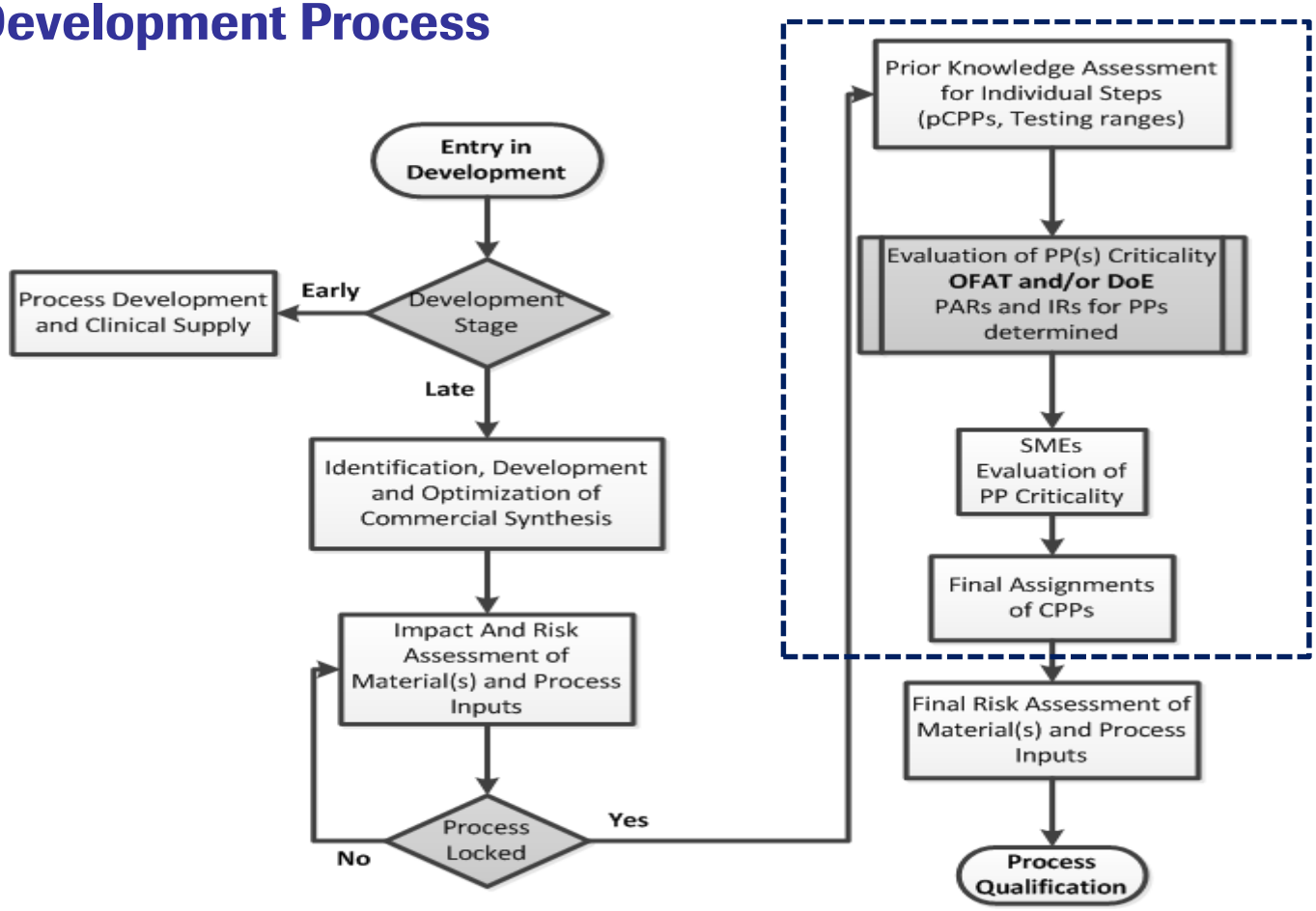
Operational Support

Best Practise Guidance: Risk assessment for the selection of starting materials
DOC NO TEC-0121148

Empiric tool that helps to assess the probability of rejection or approval of a proposed RSM by authorities.

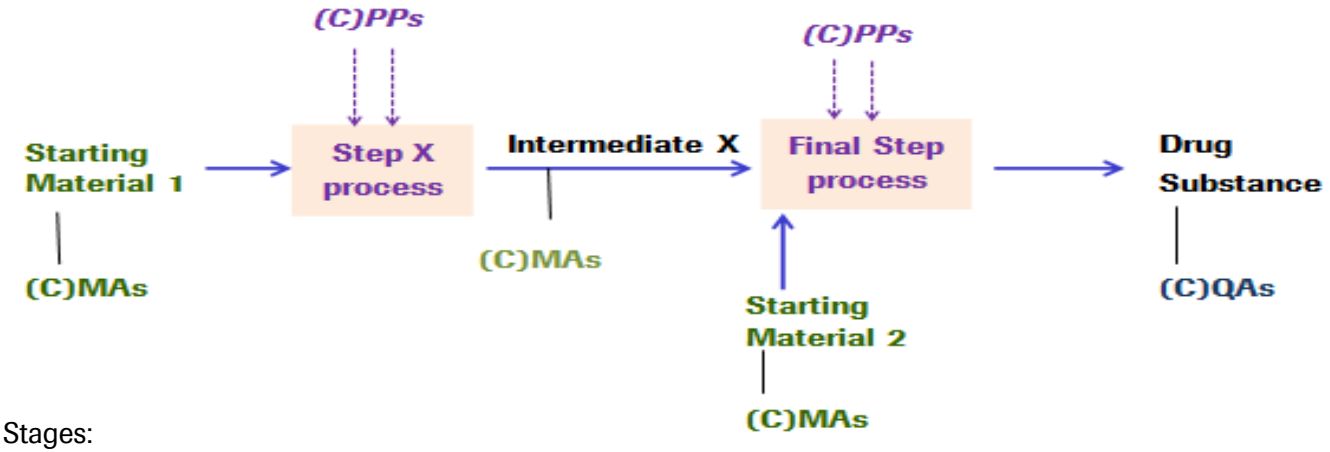
Genentech
A Member of the Roche Group
CHUGAI
Roche

Overall Development Process



Our Ideal CMO

Excursus: Compliance as Key Success Factor – Quality Risk Analysis



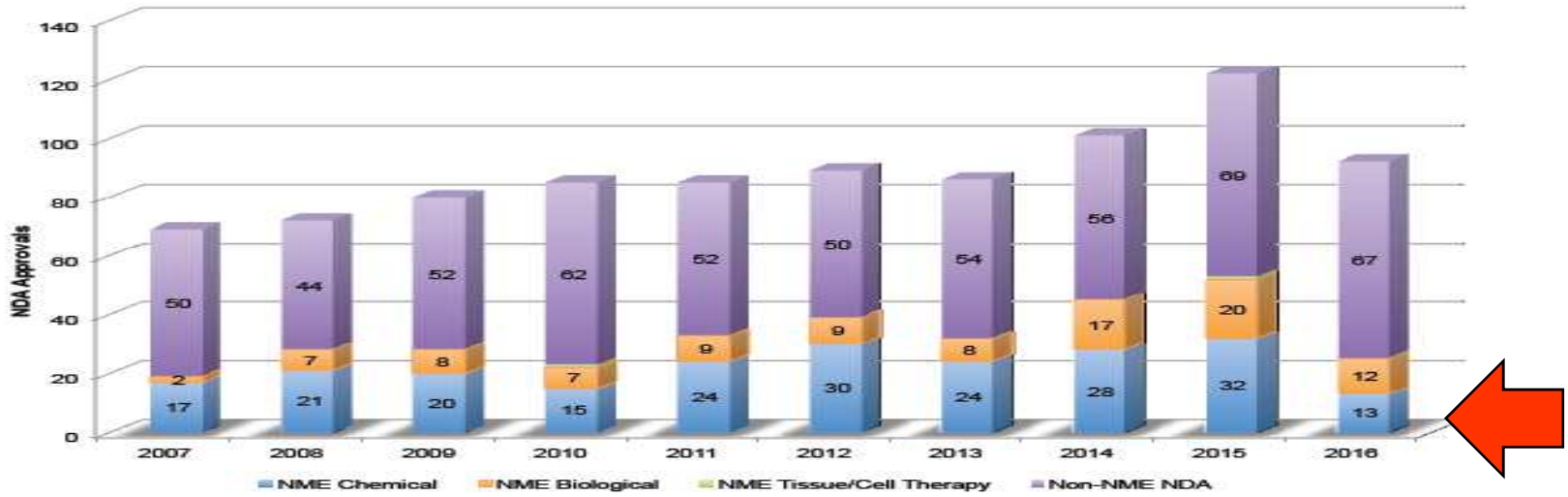
Five Stages:

1. Derive drug substance potential critical quality attributes (pCQAs) from the Quality Target Product Profile (QTPP) of the drug product.
2. Impact and risk assessment of material and process inputs; and documentation of focus areas for risk mitigation.
3. Identification of potential critical process parameters (pCPPs).
4. Evaluation of impact ratio, and final assignment of CPPs.
5. Final risk assessment of material and process inputs to determine criticality, i.e. pCMAs to CMAs, pCPPs to CPPs, pCQAs to CQAs.

CMC at Large Pharma

New Chemical Entities Launches (FDA)

Figure 1 NDA Approvals 2007-2016

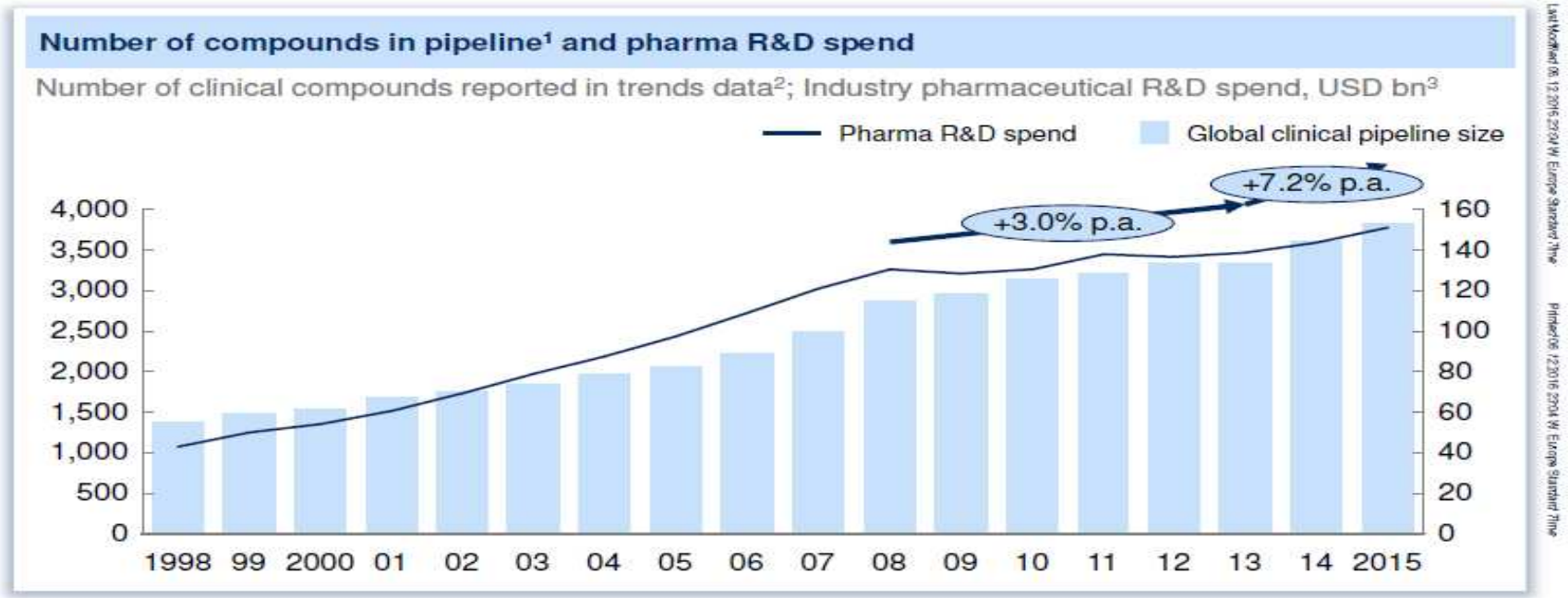


Source: PharmSource Analysis of FDA data

- The 25 NMEs approved in 2016 represented the smallest number since 2010 and a decline of almost more than half for NCEs (32 vs 13 in 2016) from 2015.
- Share of NME Biologicals increased and is now 50/50

CMC at Large Pharma

Development Projects in Clinical Phases



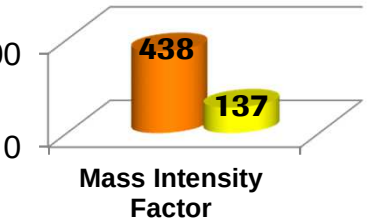
In conclusion

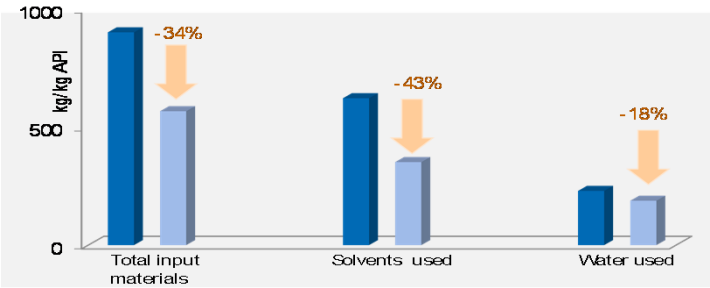
- Decreasing number of NCEs, but steady increase of new entities in clinical phase
- High attrition rate, requiring needed skill set at both ends – **Originators and CMOs**

Designing and Developing Green Processes

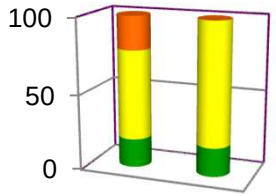
The 12 Principles of Green Chemistry

1. Prevent Waste
2. Atom Economy
3. Less Hazardous Synthesis
4. Design Benign Chemicals
5. Benign Solvents & Auxiliaries
6. Design for Energy Efficiency
7. Use of Renewable Feedstocks
8. Reduce Derivatives
9. Catalysis (vs. Stoichiometric)
10. Design for Degradation
11. Real-Time Analysis for Pollution Prevention
12. Inherently Benign Chemistry for Accident Prevention





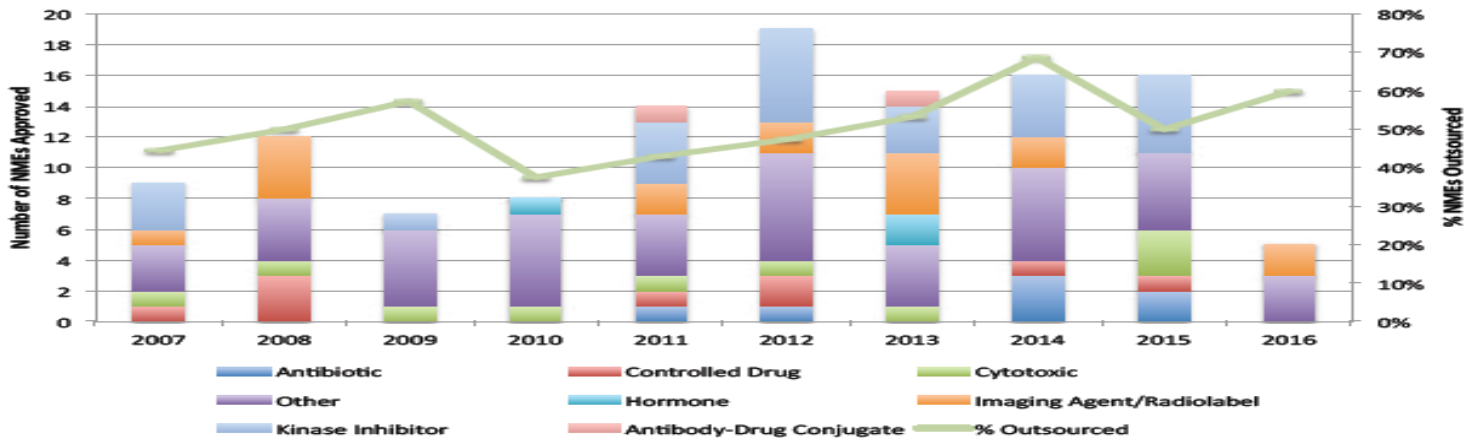
Solvent Usage	Preferred solvents	Usable solvents	Banned solvents
Initial Synthesis	19%	59%	22%
Optimized Process	19%	81%	0%



Our Ideal CMO

Excursus: Molecules requiring special handling – Technology ?

Figure 12 NMEs Requiring Special Handling 2007-2016



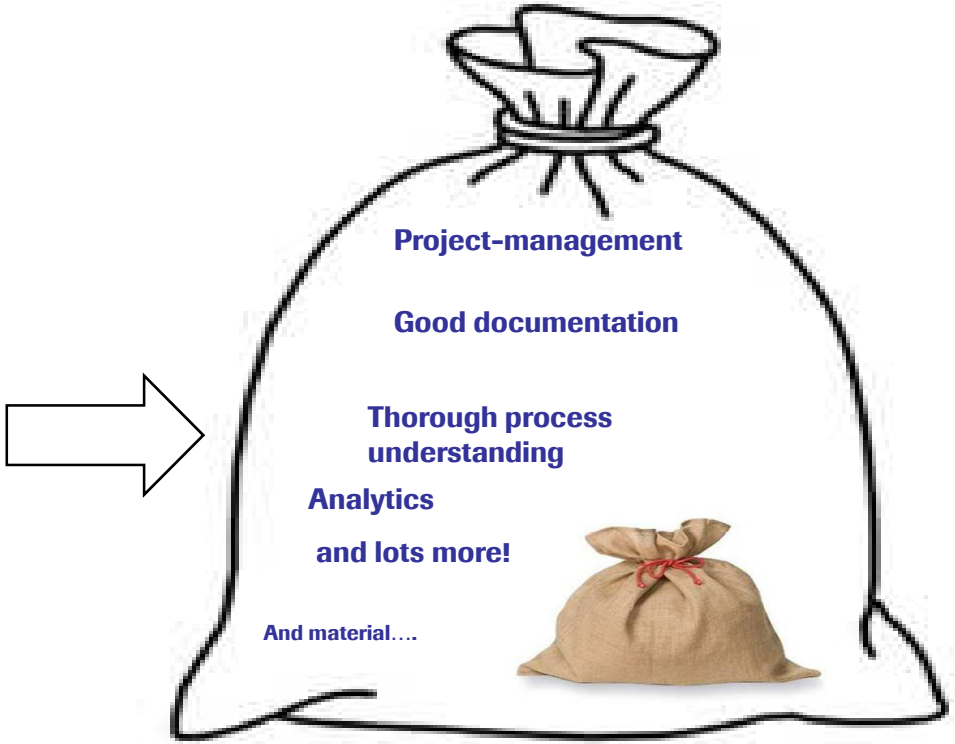
Source: PharmSource Analysis of FDA data

- Out of the 12 approved NMEs in 2016, only 5 required special handling (38%);
- Of increasing importance: High Containment facilities as a consequence of more targeted research activities

Our Partner

Expectations … what has changed since the 00'

Material



Doing now what patients need next