PDA ISRAEL
TECHNOLOGY TRANSFER AND WORKING WITH CMO/CDMP
TEL AVIV, MARCH 4TH, 2019

Connecting People, Science and Regulation

Recipharm
good for business

RECIPHARM, A CDMO ON THE GLOBAL ARENA

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Disclaimer!!

Note 1. Combined LTM June 2018 proforma revenue after Holmes Chapel acquisition

TOPICS

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CMO AND CDMO

Started as a niche market mostly for manufacture of drugs

- Final drug forms (FDF) that were special
- Additional or alternative production capacity

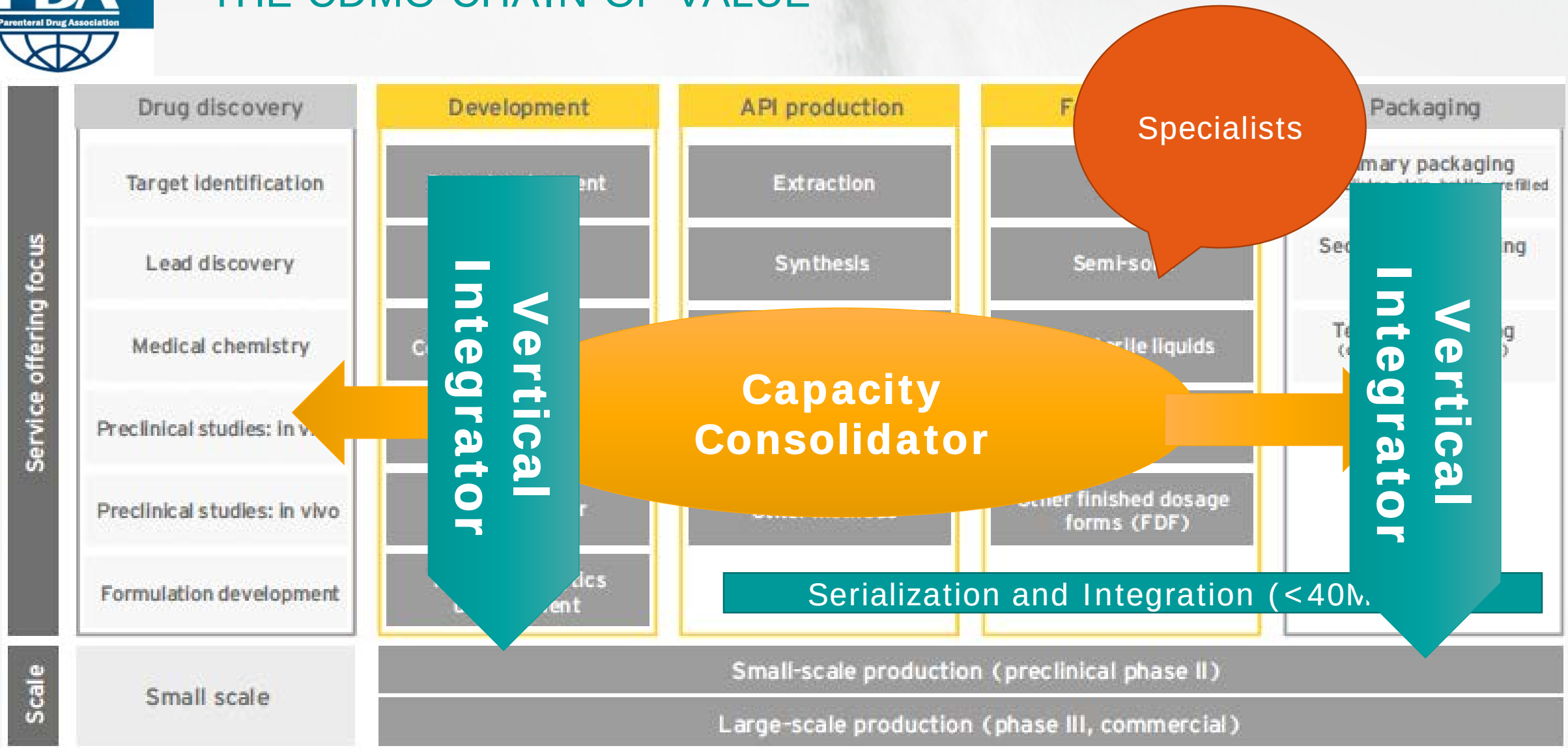
CDMO and CROs are growing faster than the pharmaceutical industry.

strong consolidation trend

Huge M&A in the end 2016

- Lonza acquired Capsugel, for $5.5b.
- Thermo Fisher acquired Patheon for $7.7b

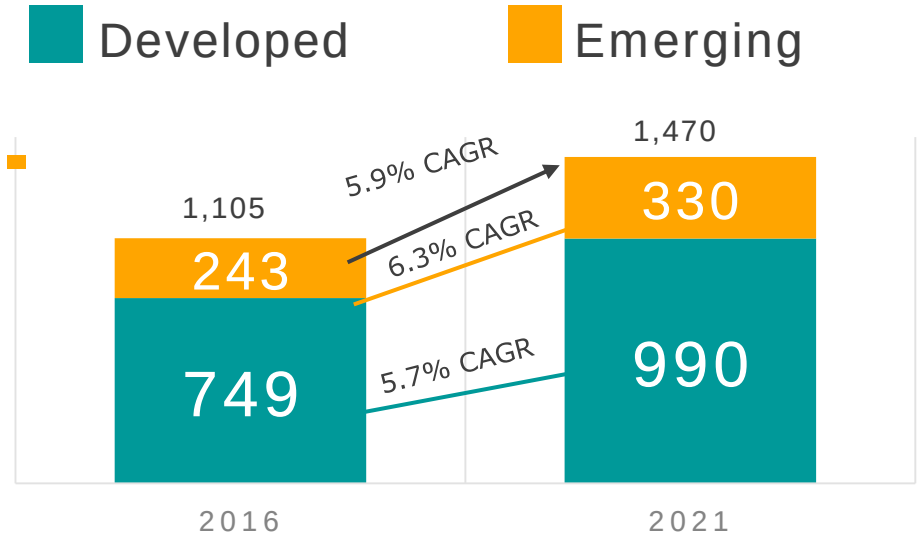
THE CDMO CHAIN OF VALUE



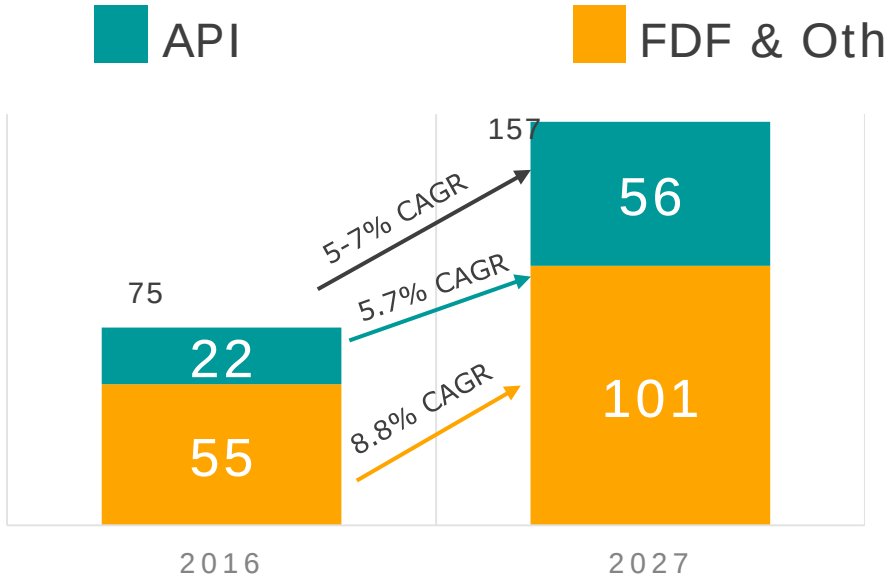
The pharmaceutical industry is consolidating EY report 2017

STARTED AS A " NICHE" MARKET, THE CDMO MARKET GROWS AT FASTER RATE THAN PHARMA INDUSTRY

Pharma market by value ($b[1])



CDMO market by value ($b)[6,7]



- NDA increased significantly lately:
  - FDA approved <5 new drugs in 2018, 46 in 2017 *vs.* only 22 in 2016[3]; and 763 generic[4]
- Almost all volume growth comes from emerging markets[1].

- CDMO grows steadily mostly API[7,6].
  - growth driven by OTC and generic products[8].

[1] Outlook for Global Medicines Through 2021: Balancing Cost and Value, IMS, December 2016; [2] EvaluatePharma World Preview 2018, Outlook to 2024, June 2017; [3] Novel Drug Approvals for 2018; [4] FDA sets another record in 2018, Dive Insight, October 2018; [5]Human medicines highlights 2017, EMA, January 2018; [6] Pharmaceutical Contract Manufacturing Market 2017-2027, Visiongain, February 2017; [7] Top 30 Pharmaceutical CMOs Market Forecast 2017-2027, Visiongain, July 2017; [8] Pharma & Biotech 2017 – Review of Outsourced Manufacturing, Results Healthcare, January 2017

OVERVIEW OF THE GLOBAL CMO/CDMO MARKET

CDMO market share worldwide

CDMO market share in the EU

In Israel lots of companies try to buy the cheapest service either from China, India or East Europe

The general assumption, same “molecule/service” lower price

South Korea – 1.9%

Russia – 1.9%

Pharmaceutical Contract Manufacturing Market 2017-2027, Visiongain, February 2017;

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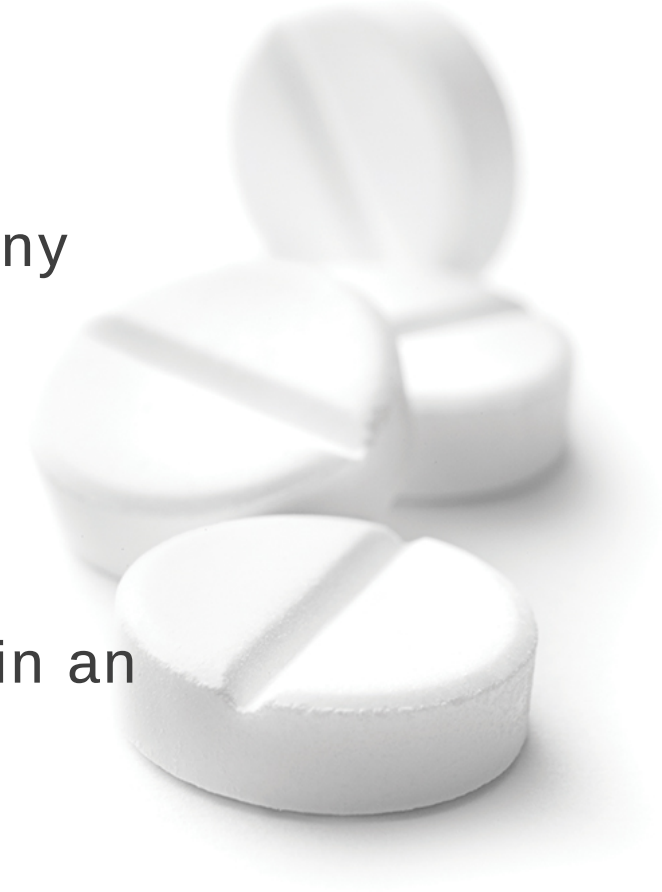

WHY LARGE COMPANIES OUTSOURCE

- Reduce Risk
  - Diversification of production sites
  - Lack of approval - E.g production line should be developed before regulatory approval
- Increase and/or diversify Capacity
- Reduce Costs
  - E.g. a production line that will function full time
- Reduce Complexity
  - E.g. Sourcing, API production and several FDF & packaging are VERY different tasks types creating complexity that is difficult to manage
- Concentrate in core capabilities in all levels
  - E.g. Today we see more R&D in collaboration with start-ups and Universities

BIG PHARMA PREFER TO PARTNER WITH LARGE CDMO/CMO

- Want fewer relationships
  - Reduce prices
  - Reduce personnel dealing with contracts
  - Longer contracts – beneficial to both sides
- Confidentiality
- Organisations who can manage complexity
  - From early development to production
  - CDMO is not only a service provider is a “collaborator”
- One-Stop-Shop strategy became one of the main drivers for M&A of CMO/CDMO

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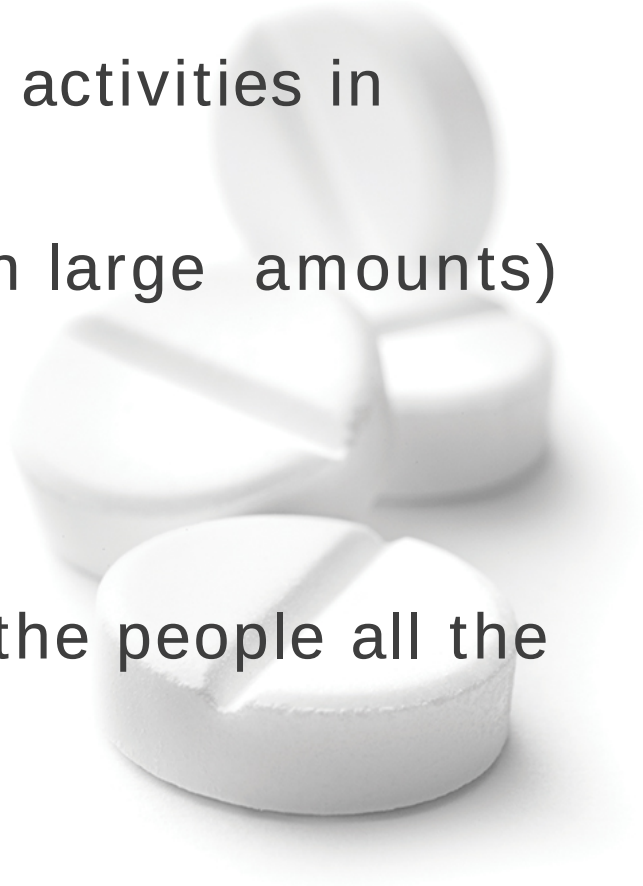
SMALL – MEDIUM SIZE COMPANIES-SME (10 TO 200 PEOPLE)

- Cost / Feasibility
  - Very expensive to establish all the development activities in house – need to choose
  - COGs are higher (CDMO buy lots of materials in large amounts)
  - Difficult to manage complexity
- Flexibility
  - Difficult to find all specialties needed
- Companies can not provide full employment to all the people all the time
- Decrease risk:
  - Production lines are established usually during Phase III



VIRTUAL COMPANIES: A DIFFERENT STORY

These companies are structured by strategy to outsource

- Strategic decision
- Saves establishment & maintenance costs
- CDMO/CMO are more "partners" than service providers
- Leaves all the work and complexity management to the "partner"

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IN HOUSE ADVANTAGES AND DISADVANTAGES

Capabilities	Advantage in-house	Disadvantage in-house	Establishment $	Personnel 3 ($/Year)
Biology *in-vitro*	Control over efficacy assays, PoC & MoA	None	50,000 to 250,000	±340,000
Biology *In-vivo*	Control over models, efficacy, toxicity, PoC,	Need Animal facility and work with animals	20,000 to 300,000	±340,000
Chemical/Analytical	Control of chemical development	Large variance in work load	1,000,000 to 3,000,000	±650,000
API Production	In-house Production of the API control	Specialized, QA, QC expensive, variance in amount of work	5,000,000 to 50,000,000	±900,000
Regulatory & logistics	Control over regulatory and logistics	None	Mainly salaries	± 325,000
Project Management	Overview only	None	Salaries	±450,000

IN HOUSE VERSUS OUTSOURCE PRICE/YEAR

Capabilities	Establishment $	personnel 3 ($/Year)	In-house	Outsource	Outsource Advantage
Biology *in vitro*	50,000 to 250,000	±340,000	±730,000	± 3,750,000	Speed, Expertise
Biology *In vivo*	20,000 to 300,000	±340,000	±850,000	±3,375,000	Speed, Expertise
Chemical/Analytical	1,000,000 to 3,000,000	±450,000	±2,200,000	±3,000,000	Speed, Expertise, Flexibility
API Production GMP/GLP	5,000,000 to 50,000,000	±900,000	+11,000,000	Depending on project 0.5 to 3M	Speed, Expertise Flexibility
Regulatory & Logistics	Mainly salaries	± 325,000			
Project Management	Salaries	±450,000			

Cost of establishment: average/3

You pay only what you need

WHAT TO OUTSOURCE

If you decide to outsource part/all of the company activities ask yourself

- Define your core technology
- Define your company Aim/Vision/Exit or Growth Strategy
- Define your “dream product” and market
- Define your budget
- Be realistic, even pessimist with your possibilities
- If you want to keep in-house activities, define which expertise you can hire and keep
- Do a thorough risk assessment of each part

Then and only then decide what do you want to outsource

EXAMPLE – DEVELOPMENT OF AN INDUSTRIAL ENZYME

Define your core technology	Directed Molecular Evolution
Define your company Aim/Vision/Exit-growth strategy	to develop a super enzyme and sell the rights to one of the three big enzyme companies
Define your "dream product" and market	A high active galactosidase enzyme working at pH 7 – market world wide
Define your budget	4M USD
Be realistic even pessimist with your possibilities	Possible to develop in two years, then pilot will take one year and be outsourced
Define which expertise you can hire and keep	Biochemist – Molecular Biologist this will keep the core technology and PoC in-house
Risk Assessment	Feasible at all steps
The three big enzyme companies were interested – **But** offered to start the development in 6 years from signature, and 3% royalties if possible to sell for less than USD 10Kg	

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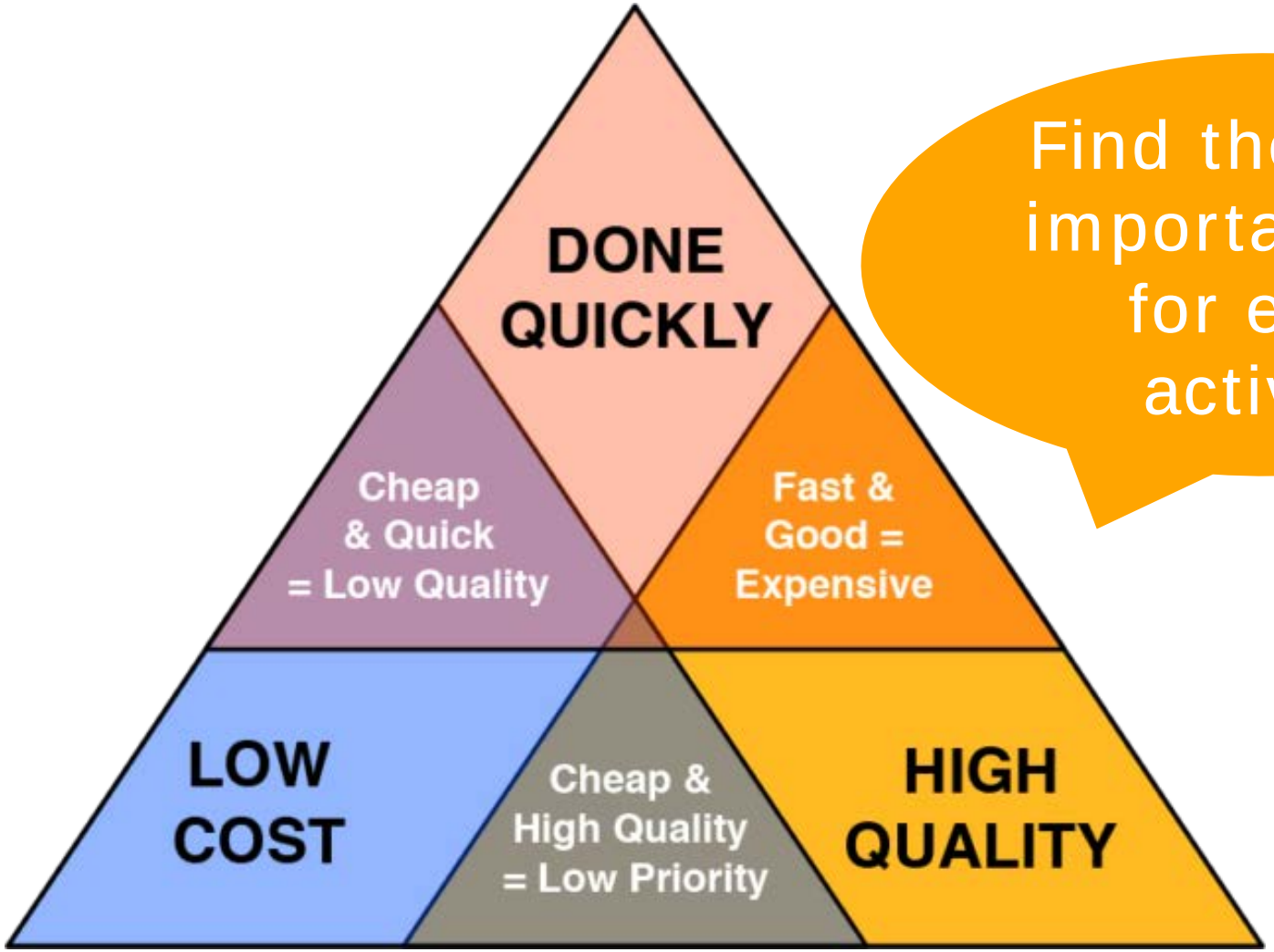
HOW TO CHOOSE THE “RIGHT” CDMO FOR YOU

- Ask several CDMOs if they can produce the kind of molecule you have (some CDMOs will not do for e.g. hormones)
- Do you prefer to work with very large / large or medium size companies
- Do you prefer one-stop shop or several companies /locality
- Ask peers about: flexibility, quality, support, transparency, communication & tenacity, audit of sourcing materials providers
- Don’t ask if they were happy with the results – sometimes the client gives not enough information, sometimes CDMO fails
- Remember TT between companies takes time (from 6 to 7 months) and cost money – sometimes to change CDMO in API from Phase II to Phase III

TOP 20 CDMOs

№	Company	Corporate HQ	Ownership	Revenue, $ million	Headcount
1	Lonza	Switzerland	Public	5,209 (2017)[1]	14,882
2	Patheon, part of Thermo Fisher	USA	Public	7,825[2]/2,582[3] (2017)	12,000 (Pharma Service)
3	Catalent	USA	Public	2,463 (2018)	10,700
4	Siegfried	Switzerland	Public	766 (2017)[1]	2,300
5	Aenova	Germany	Private equity	~750[4,5]	4,300
6	Pfizer Centre One	USA	Subsidiary of public pharma	706 (2017)	-
7	Recipharm	Sweden	Public	704 (Q3 2018 LTM)[6]	~6,000
8	Almac	UK	Private	681 (2017)[7]	4,407
9	Boehringer Ingelheim BioXcellence	Germany	Private	678 (2017)	-
10	Vetter	Germany	Private	635 (2017)	4,400
11	Fareva	France	Private	~630 (2017)[4,8]	~5,400[7]
12	Nipro pharmaceutical	Japan	Public	622 (2017)[9]	-
13	PCI Pharma services	USA	Private equity	600 (2017)	3,200
14	AMRI	USA	Private equity	571 (2016)	3,085
15	Delpharm	France	Private	565 (2017)	3,200
16	Cambrex	USA	Public	535 (2017)+105 Halo	1,228+450 Halo Pharma
17	Baxter Biopharma Solution	USA	Subsidiary of public pharma	455 (2017)	-
18	Famar	Greece	Private	434 (2016)[10]	2,900
19	Corden Pharma	Germany	Private	390 (2017)	1,870
20	Consort Medical (Aesica)	UK	Public	398[11]/236[12]/ (2018)[7]	2,060

HOW TO CHOOSE THE "RIGHT" CDMO FOR YOU



Find the most important two for each activity

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IN A QUOTE FOR FTE R&D PROJECT PAY ATTENTION TO:

What is included in the quote

- Sourcing – Overhead - how much?
- Analytics – will be included or invoiced separately all the analytics needed
- CoA - how it will be done and what will include
- Chemicals disposal – ask if included/price
- Kits needed
- Columns
- What is not included should be clearly stated
- Reporting level – can you repeat the process in any other lab
- How will be the interaction – communication is the key
- Flexibility & Availability

IN A QUOTE FOR API PROJECT PAY ATTENTION TO:

What is included in the quote

- Literature analysis of “dangers” of final products and intermediates
- Sourcing – Overhead - how much? / Audited? Included?
- Analytics – Method Development - very important step, all other needs of Analytics including for development
- Impurities – identification and synthesis how many of them?
- Is the CDMO complying with **your** market regulatory requirements?
- Chemical disposal included?
- Kits needed, columns, disposables
- What is not included should be clearly stated
- Communication, frequency, mode
- Flexibility & Availability
- Technical Transfer if needed to a manufacture or other – included?
- Storage, insurance and shipment

DON'T FORGET:

- Companies have contracts for months if not years ahead – plan with time even if you don't have the final conditions
- API – A technical batch is always made - ask to make enough amount and to receive it - use it in toxicology – will save you a lot of money
- API & Clinical trial material – plan ahead time and leave time for problems – they always appear
- Work with one provider for all the clinical trials materials from Phase I to Phase III. Changing in the middle can cost you more than producing the API
- Serialization & Aggregation are requirements look for a flexible supplier that can comply with all your markets needs there are differences

SOME EXAMPLES OF “CHEAP QUOTES”

Problem found	Cause
The impurities identities and/or amounts in the final product different than in development	Low quality raw materials carrying impurities changed the results of the reactions
	Intermediates not purified as indicated by the protocol but using cheaper method
	Heat applied to accelerate reactions create unexpected impurities
Yields much lower than expected	Heat applied to accelerate reaction creating problems in the yield
Product not received by client	CDMO in China being closed O.N. for not complying with safety regulations
	Vials used to lyophilize the final product were of low quality and crack – Audit of suppliers!
Price much higher than expected	Not all cost clearly explained. Analytics not included meant that every HPLC/LC MS done were charged in addition to the cost

IDEAL PROCESS DEVELOPMENT WILL YIELD

- Low number of chemical steps
- High yield in each step
- Low amount of impurities
- Purification compound without the use of columns
- Re-use of solvents – close system if possible
- Solvents considered not dangerous by the industry
- Short time in the production line

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FROM MG TO KG OF DRUG SUBSTANCE IS A CHALLENGE

250 mL
(preclinical)

50 L
(clinical)

6000 L
(commercial)

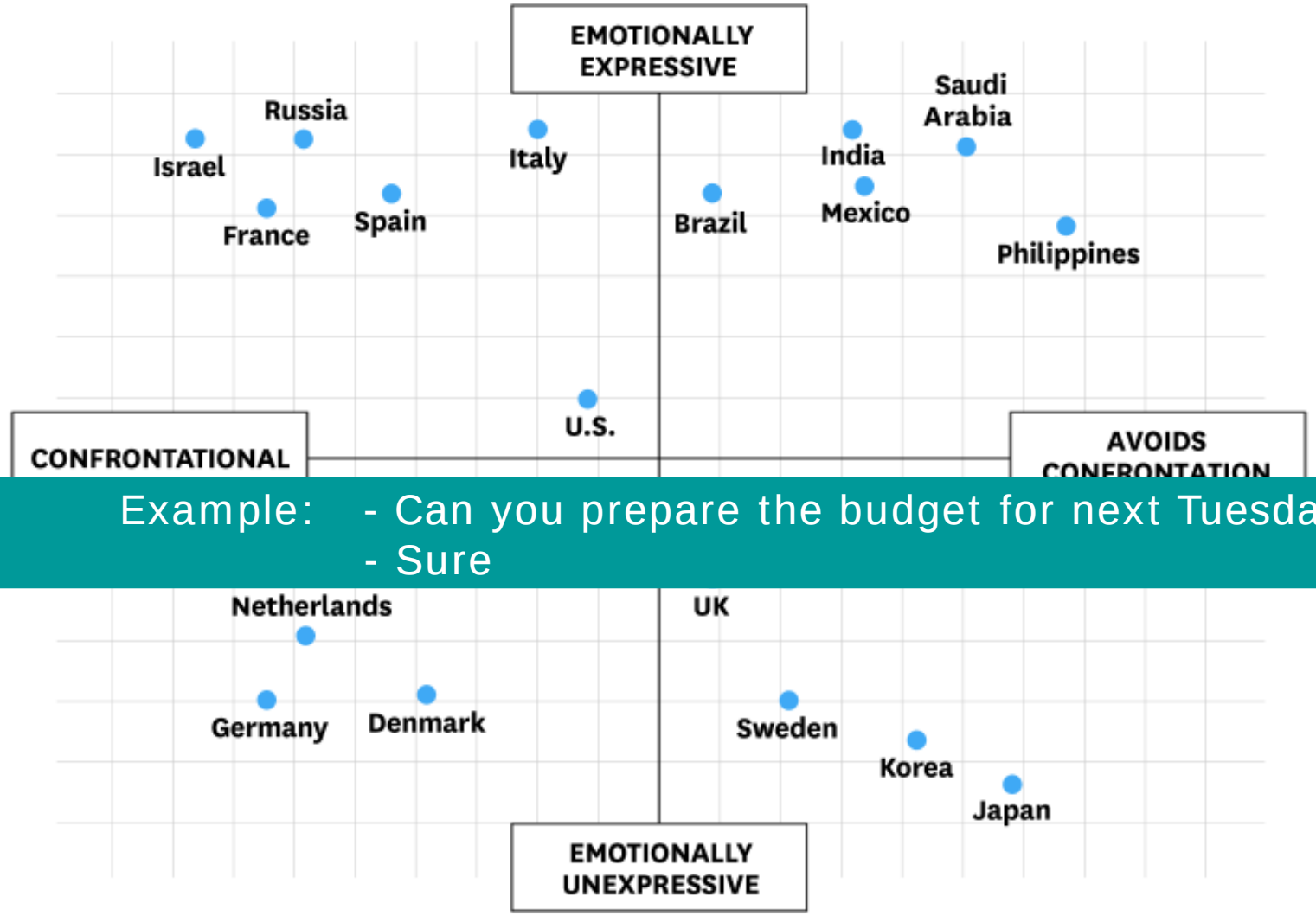
NOT ONLY A TECH CHALLENGE

- 10 different countries
- 9 different languages (at least…)
  Swedish, English, German, French, Portuguese, Spanish, Italian, Hindi, Hebrew, …
- >10 hours time difference
- Other differences:
  - Office hours
  - Vacation periods
  - Religious holidays
  - Lunch, Dinner times
  - Meeting culture and others

In most companies

And this in only one company

CULTURAL DIFFERENCES



Example: - Can you prepare the budget for next Tuesday
- Sure

SOURCE ERIN MEYER
FROM "GETTING TO *SÍ, JA, OUI, HAI,* AND *DA*," DECEMBER 2015

© HBR.ORG

“Poor communication & assumptions: the Mother of all failures”

Solution: Define clear process

TECH TRANSFER PROCESS - STRUCTURE

Transfer from Developing Site to Receiving Site (RS)

Month 1 — **Initiation**

- Kick-off meeting with RS
- Establishment of project team
- Project admin documentation (e.g Communication Plan, Action Plan, ShareP
- **Review RACI (D)**
- Formulation Develo Protocol **(D)**
- Draft Tech Transfer P **(D)**
- Draft Product Description Report **(D)**
- Risk Assessment **(D)**
- Draft Anal Methods **(D)**

Month 2-3 — **Information transfer**

1

- Final TT Plan **(D)**
- Final Product Description **(D)**
- Draft Specification DP
- Analytical Method Transfer Protocol **(D)**
- Analytical Method test run

Month 4-6 — **Execution**

2

- Analytical Method

Month 6-7 — **Completion**

- Pharmaceutical Development Report **(D)**
- nalytical Transfer eport **(D)**
- essons Learned (after alidation batches) **(D)**

In Recipharm: 16 document templates must be filled from Development to manufacture – same company

n transferred?
Correctly percieved ar RS?

2 Checkpoint: Distribution of Pharmaceutical Development Report to RS

(D) Document Template

Recipharm good for business

RACI MATRIX FILLED IN EACH STEP AND STEP

- **R = Responsible** - Those who do the work to complete the task
- **A = Accountable** (also Approver) - The *accountable* must sign off (approve) work that *responsible* provides
- **C = Consulted**
- **I = Informed**

Task	QA	Project manager	Commercial manager	Operations
Do this	A	C	I	R
Do that	R	A	I	C
Report	C	R	I	A
Follow up	I	R	A	C

FOR A SUCCESSFUL TECH TRANSFER/SCALE UP

- Don’t underestimate the complexity and time required
- Clarify responsabilites and expected timelines
- Define clear processes
- Don’t hide any detail – if you don’t fully trust your service provider don’t work with it/her/him

THANK YOU FOR YOUR ATTENTION

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