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A CRO perspective of the Pharma-CRO relationship

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Overview

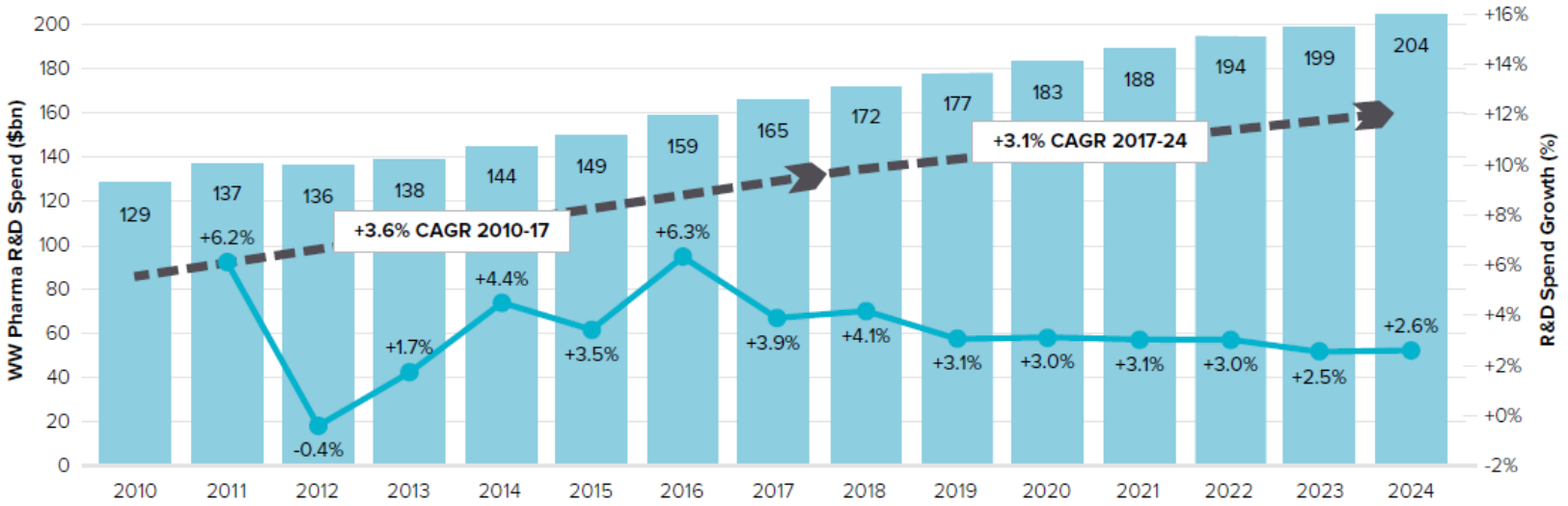
- Background
- Focus on crucial steps
  - Actors & information
  - Samples
  - Method
- Case studies

Pharma R&D Spend

- Average forecast R&D spend to pharmaceutical revenue: 19.5% btw 2010 and 2017, 18.9% in 2024
- Need of improving R&D efficiencies

Worldwide Total Pharmaceutical R&D Spend in 2010-2024

Source: Evaluate, May 2018



Pharma R&D Outsourcing



Extent of Outsourcing

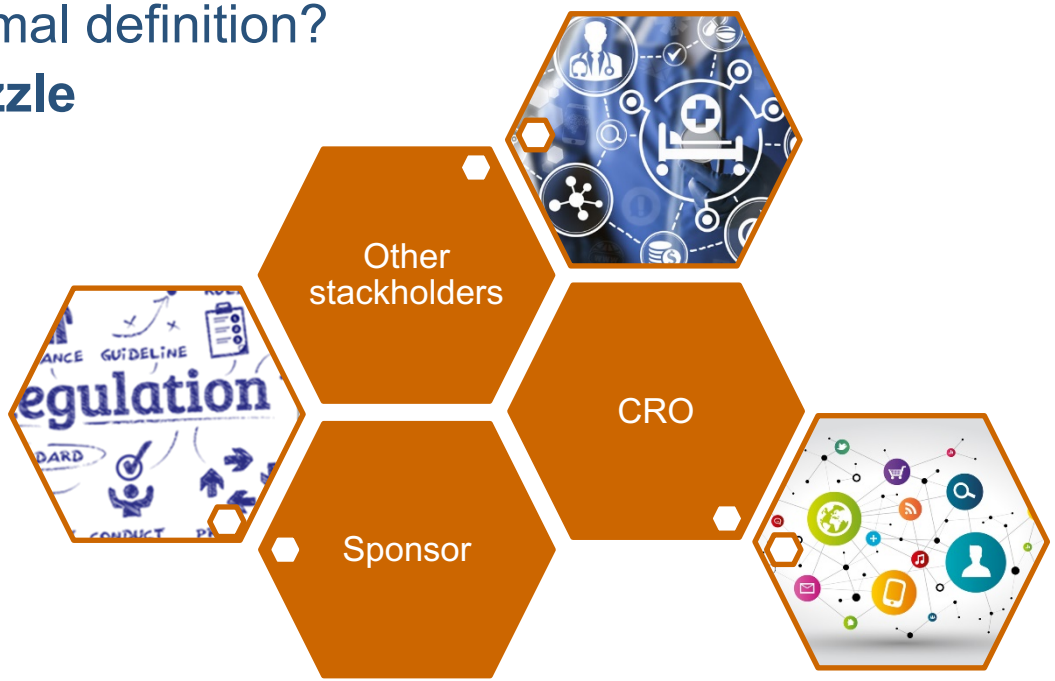
Offshored activities

Opportunity Analysis	Drug Research	Discovery	Development	Registration	Launch / Marketing
Competitive intelligence Business intelligence Market research	Functional genomics Lead identification	Discovery chemistry	Preclinical Clinical trials	Material preparation	Analytics

Outsourcing

- Definition on Google:
  Obtain (goods or a service) by contract from an outside supplier

- What is beyond this formal definition?
  Putting together a puzzle



Outsourcing

PROJECT MANAGEMENT

Communication
Planning
Resources
Equipment
Timelines
Budget
Flexibility
KPIs

TECHNICAL

Expertise
Study design
Development
Validation
State of the art
Sample management
Data transfer
Reporting

REGULATORY & QUALITY

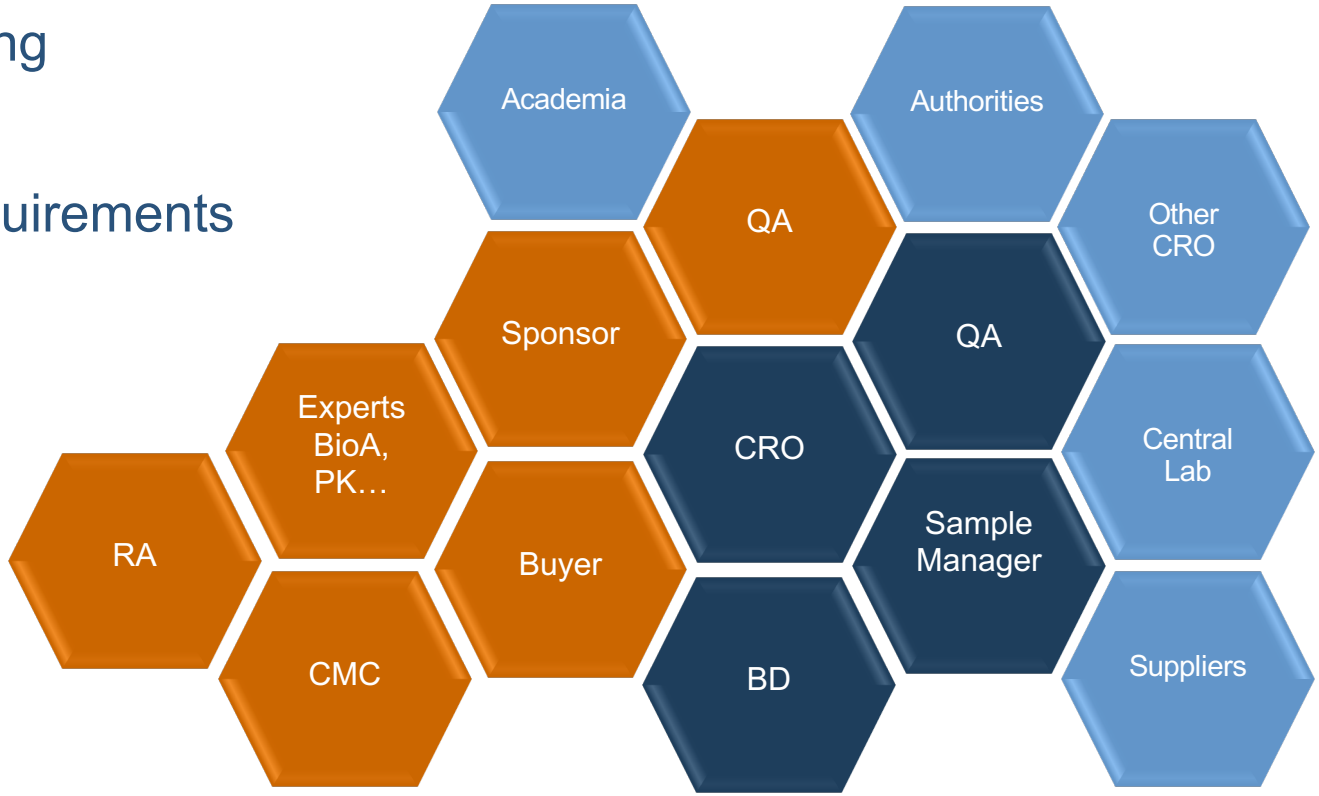
GLP
GCP
GMP
EMA
FDA
PMDA
ANVISA
Guidelines
Data integrity

Outsourcing

- **Building a strong relationship** is the key for outsourcing projects
- Relationship based on:
  - Teamwork and trust
  - Shared vision
  - Open communication
  - Good personal relationship
  - Understanding perspective
  - Mutual respect
  - Common commitment

Information & actors

- Method requirements
- Analytical standards & CoA
- Sample handling
- Stability data
- Regulatory requirements
- …

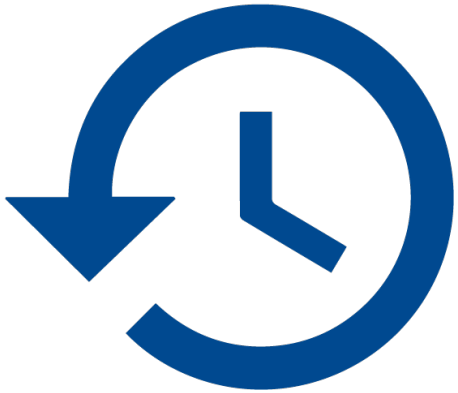


Initiation of the partnership

- Partnership starts with a request
- Often managed by BD/commercial team, supported by experts
- Establishment of a contract corresponding to the request
- Need to speak the same language
- Setup the communication tools
  - E-mail communication
  - F2F meetings
  - TC, webex

Timelines

- Management and respect of timelines are the crux of any projects
  - Dedicated project manager and team
  - Updates at predefined frequency
  - Use of project management tools (Gantt…)
  - Communication of any issues and delays
  - Knowledge of the whole project pipeline to prioritize outsourced activities



Sample management

- Collection specifications and precautions are not always clearly defined at the initiation of a pre-clinical/clinical study
- Implement an open communication as soon as possible during protocol drafting
- Practical limitations have to be considered during method development
  - Materials (tubes, pipettes, centrifuges, freezers…),
  - Ready-to-use commercial tubes or preparation,
  - Toxicity of stabilizer…

Sample management

- Define, in the protocol, SOP or separate document (*e.g.* lab manual), the sample collection and identification details:
  - Collection tube and anticoagulant,
  - Labelling and information,
  - Number and volume of aliquots,
  - Sample process,
  - Collection precautions (temperature, duration) according to stability data,
  - …

Sample management

- Ensure storage conditions at each step, from sampling to long-term storage, including shipment and analysis
  - Sampling files
  - Shipment data logger
  - Bioanalysis data
  - Freezer monitoring
- Ask for import permise
- Check compliance of sample tube identification and files provided along with samples, to ensure data integrity

Method transfer

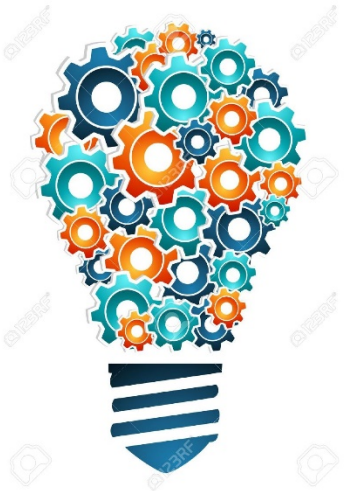
- Same language, same guidelines... but own practices
- Method transfer from Pharma to CRO (or between CROs) should be anticipated to ensure:
  - Project timelines,
  - Data reliability,
  - Sample and data integrity
- Smooth method transfer can be achieved when detailed instructions are shared (analytical procedure and overlooked details)
  - Avoid interpretation of the method
  - Clarify any points

Method transfer

- Define the transfer procedure:
  - Has the method been modified?
  - What do guidelines state?
  - Which tests have to be included?
- Method transfer allows to assess the robustness of the method
- Slight differences may have a significant impact on the method performances and robustness:
  - Environment conditions,
  - Process,
  - Materials,
  - Instruments…

Innovation

- Innovation is fundamental to improve R&D, initiated by need or new idea (Pharma, CRO, academia, supplier)
  - Process innovations: sample and data management, scientific validation approach, automation…
  - New technologies to save time and/or improve data quality
  - Driving innovations: patient (sample volume, sampling techniques), regulatory…
- Risk is part of innovation, and this risk has to be known and shared by all involved parties
- Regulators have to be involved in innovation, to accept it and implement guidelines



Case study #1

- Transfer of a validated method for the assay of a drug and its metabolites in human plasma
- Analytical standards provided as free base according to CoA
- Review of the protocol of dose escalation study in human
  - Same batch administered to subjects
  - Identified as a chlorhydrate salt
- Confirmation by the Sponsor of the salt form of the API (also used as analytical standard)
  - Request for a statement or an updated (and corrected) CoA
  - Correction of all validation data (reprocess and update of the SOP)

Case study #2

- Development and validation of a semi-automated method for the assay of one drug in human plasma
- Requirement of use of 2D-barcoded 96-format cryotubes
- Review of lab manual for implementation of the tubes
- Reception of first plasma samples to be assayed:
  - Samples stored in labelled 2D-barcoded 96-format cryotubes, stored in 10-mL PP tubes
  - Samples identified with 3 different codes
- Samples to be rearranged to be compatible with 2D-barcode reader and automate
- Risk of thawing and data integrity

Case study #3

- Transfer of a validated method for the assay of lidocaine in mini-pig plasma, to support pre-clinical PK studies
- Assay of PK samples: Concentrations found to be 10 times lower than for a previous PK study
- Investigation:
  - Validation and transfer data
  - Procedures applied for blood sampling
  - Materials used for in-life phases
- Tests of adsorption in blood and plasma using the different tubes and stoppers
  - Results due to adsorption of lidocaine into collection tubes used for storage of plasma samples

Case study #4

- Development and scientific validation of a method to assay letrozole in rat plasma to support pre-clinical studies (BA, formulation screening), with a LLOQ of 0.1 ng/mL (Sponsor requirement)
- In-life phase in rat: several formulations, doses and administration routes
- Assays with calibration range of 0.1 to 50 ng/mL:
  - Group 1 (IV): all samples within range
  - Groups 3 to 8 (SC): more than 75% of samples higher than the ULOQ, up to 500 times ULOQ
- Options: Dilution *vs.* high range validation
- Re-validation of the method for High range for ethical and scientific reasons

Case study #5

- With a strong partnership, early PK studies can be managed efficiently, for the screening of drug substances or formulation
  - Quick communication
  - Reliable results
  - Quick turnaround time
  - Cost optimization

WEEK 0

- Receipt of test item
- Acclimatization phase

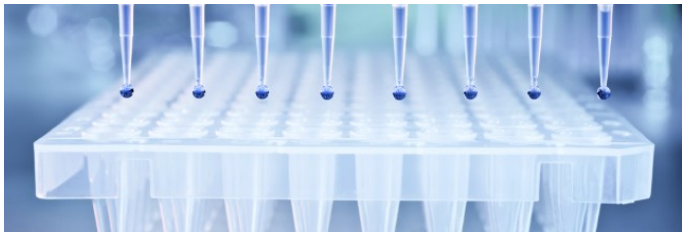
WEEK 1

- In-life phase
- Analytical method testing

- Assays of specimen
- PK interpretation
- Reporting

Conclusion

- A good communication is fundamental for a meaningful partnership between Sponsor and CROs
- Communication tools have to be adapted to each project, depending on needs of involved actors
- Bioanalysis is not always a smooth journey, but what is better than working together for managing and solving analytical issues?
- Keep communicating, communicating, communicating…



Thanks for your attention

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