An Introduction to the DDMoRe Foundation

- **Who we are**

- Where have we come from

- Where we are going to

- What have we done

- What we would like to do

- How can you help

Who are we: The DDMoRe Foundation Board and Team

Marylore Chenel

Mats Karlsson

Paolo Magni

Peter Milligan

Wendy Aartsen

Stuart Moodie

Who are we: The DDMoRe Foundation Partners and Contributors

- Industrial: + 3 others in discussion

- Academic: + 1 other in discussion

  University of Pavia

- Regulatory: in discussion with 3 agencies

- Software: in discussion with 3 analysis tool developers

Who are we: The DDMoRe Foundation Language Community Group

Mike Smith
(Pfizer)

Industry

- Malidi Ahamadi (Merck)
- Nadia Terranova (Merck)
- Amy Buchwald (Noven)
- Stayaprakash Nayak (Pfizer).
- Satoshi Shoji (Pfizer)
- Mike K Smith (Pfizer)
- Akiyuki Suzuki (Pfizer)
- Camille Vong (Pfizer)
- Chenhui Deng (Pfizer)
- Vincent Croixmarie (Servier)

CRO / SME

- Christian Laveille (Calvagone)
- Maciej Swat (Certara)

- Bill Denney (consultant)
- Stuart Moodie (Eight Pillars / DDMoRe)
- Kyle Baron (Metrum)
- Justin Wilkins (Occams)
- Celine Sarr (Pharmetheus)
- Christian Flandorfer (Scinteco)
- Ruben Faelens (SGS)

Academia

- Nick Holford (Auckland)
- Roberto Bizzotto (CNR)
- Andrea Mari (CNR)
- Charlotte Kloft (FUB)
- Frederic Bois (INERIS)
- Vincent Climent

(INSERM)

- Lisbeth DeLange (Leiden)
- Vijay Ivaturi (Maryland)
- Zinnia Parra Guillen (Navarra)
- Letizia Carrara (Pavia)
- Paolo Magni (Pavia)
- Rikard Nordgren (Uppsala)
- Gunnar Yngman (Uppsala)
- Tingjie Guo (VUMC, Amsterdam)
- Duy Tran (Thomas Jefferson University)

Who are we: The DDMoRe Foundation Repository Community Group

ddmore
FOUNDATION

Celine Sarr
(Pharmetheus)

- Mike K Smith (Pfizer)
- Akiyuki Suzuki (Pfizer)
- Amit Taneja (Kinesis-Pharma)
- Amy Buchwald (Noven Pharm.)
- Andre Jackson (Howard U.)
- Camille Vong (Pfizer)
- Dean Bottino (Takeda)
- Divakar Buddha (Excelra Know. Sol.)
- Donato Teutonico (Servier)
- Elizabeth de Lange (Leiden U.)
- Hoa Nguyen (Boehringer Ing.)
- Hwi-yeol (Thomas) Yun (Chungnam Nat. U.)
- Joachim Grevel (Bast)
- Julie Bertrand (INSERM)
- Justin Wilkins (OCCAMS)

- Letizia Carrara (U. Pavia)
- Lutz Harnisch (Pfizer)
- Maria-Luisa Sardu (Certara)
- Mike Beer (Scinteco)
- Peter Bonate (Astellas)
- Satyaprakash Nayak (Pfizer)
- Siv Jonsson (U.Uppsala)
- Stacey Tannenbaum (Astellas)
- Stuart Moodie (Eight Pillars)
- Wendy Aartsen (Hands4Grants)

Who are we: The DDMoRe Foundation Thoughtflow Community Group

![ddmore FOUNDATION]

Justin Wilkins
(Occams)

The Thoughtflow Community Group is just starting out, but core team members include:

- Pete Bonate (Astellas)

- Amy Buchwald (Noven)

- Vijay Ivaturi (University of Maryland)

- Andreas Lindauer (SGS Exprimo)

- Satyaprakash Nayat (Pfizer)

- Hoa Nguyen (Boehringer Ingelheim)

- Mike K Smith (Pfizer)

- Stacey Tannenbaum (Astellas)

- Duy Tran (Thomas Jefferson University)

- Ed Watson (AstraZeneca)

- Who we are

- **Where have we come from**

- Where we are going to

- What have we done

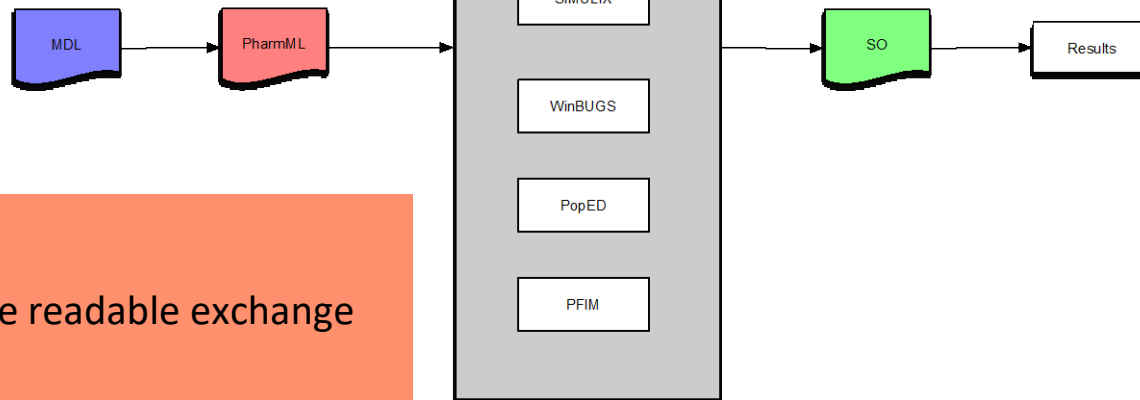- What we would like to do

- How can you help

DDMoRe Consortium "Inheritance": Products and associated products
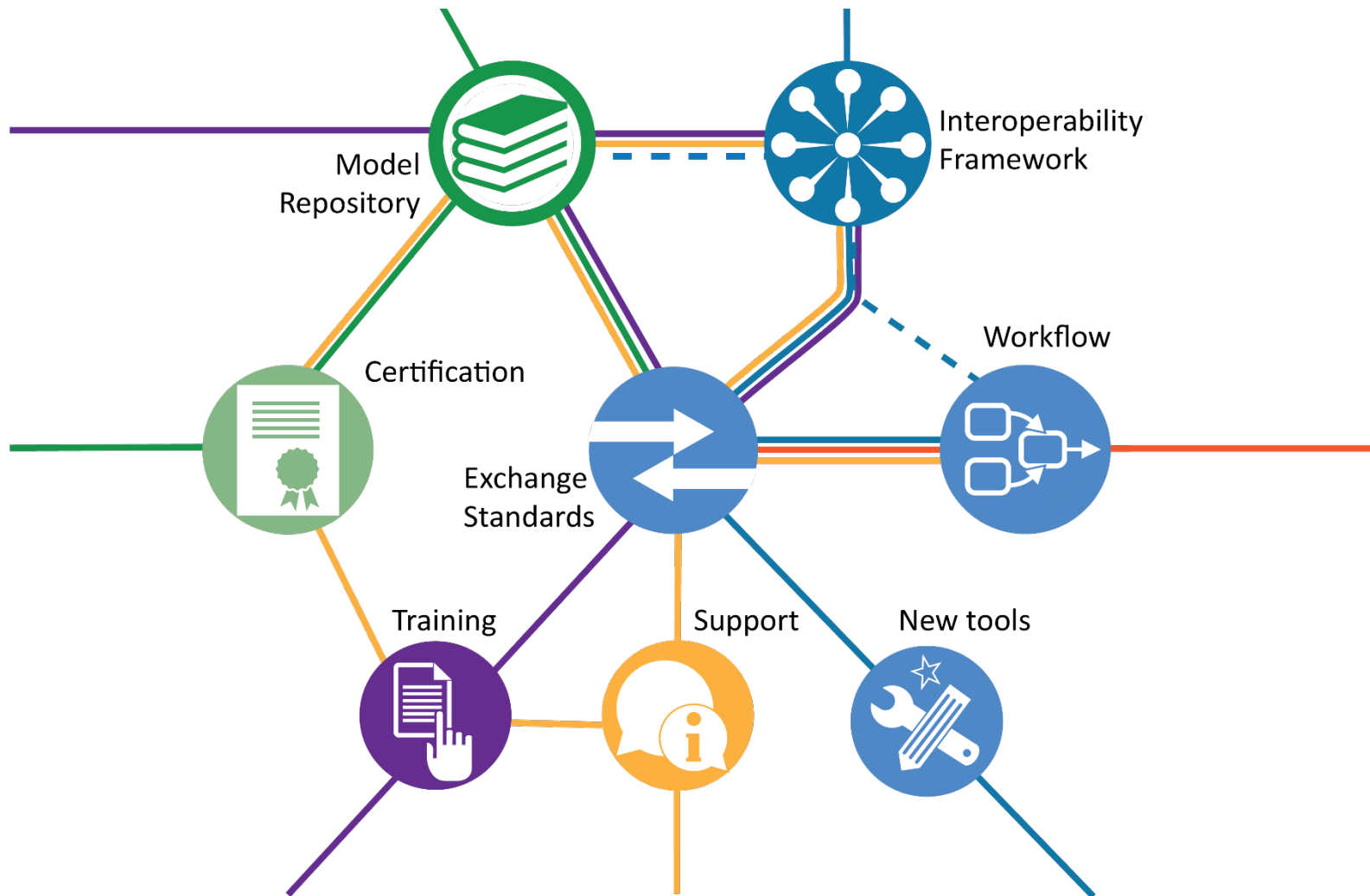
DDMoRe Consortium: Exchange Standards

Model Definition Language (MDL)
- Human readable modelling language
- Compatible with PharmML

Standardised Output (SO)
- Universal standard to capture results from multiple tools.
- XML machine readable
- Extension to PharmML

PharmML
- XML machine readable exchange standard
- Compatible with MDL
- Compatible with language converters

Tool Executors
- NONMEM
- MONOLIX
- SIMULIX
- WinBUGS
- PopED
- PFIM

MDL → PharmML → [Tool Executors] → SO → Results

DDMoRe Consortium: Interoperability Framework

- Toolset that makes interoperability a reality
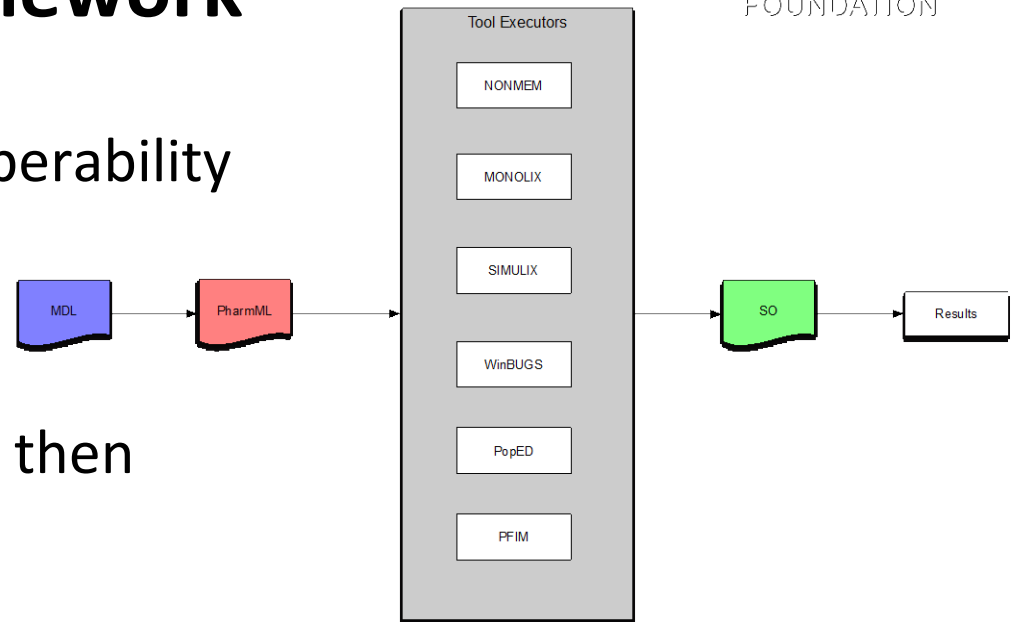
- Write a model in MDL and then execute in many tools

- Runs on Windows

Release	Functionality	Target tools	Model Types
Public Beta/ Pilot (0-2)	Estimation (NONMEM, Monolix) Bootstrap (NONMEM) VPC (NONMEM) Simulation (Simulix)	MDL Draft 7 PharmML 0.6.1 MDL-IDE 1.2.0 Monolix 4.3.2 NONMEM 7.3 Simulix 2.1.1	Continuous Count TTE
Public	Estimation (NONMEM, Monolix, WinBUGS) Bootstrap (NONMEM) VPC (NONMEM) Simulation (Simulix, SimCyp) Optimal design (PFIM, PopED)	MDL v1.0 PharmML 0.8.1 MDL-IDE 1.5.0 Monolix 4.3.2 NONMEM 7.3 Simulix 2.1.1 WinBUGS 1.4.3 PFIM 4.0 PopED 0.3.0	Continuous Binary Count Categorical TTE Prior Distributions

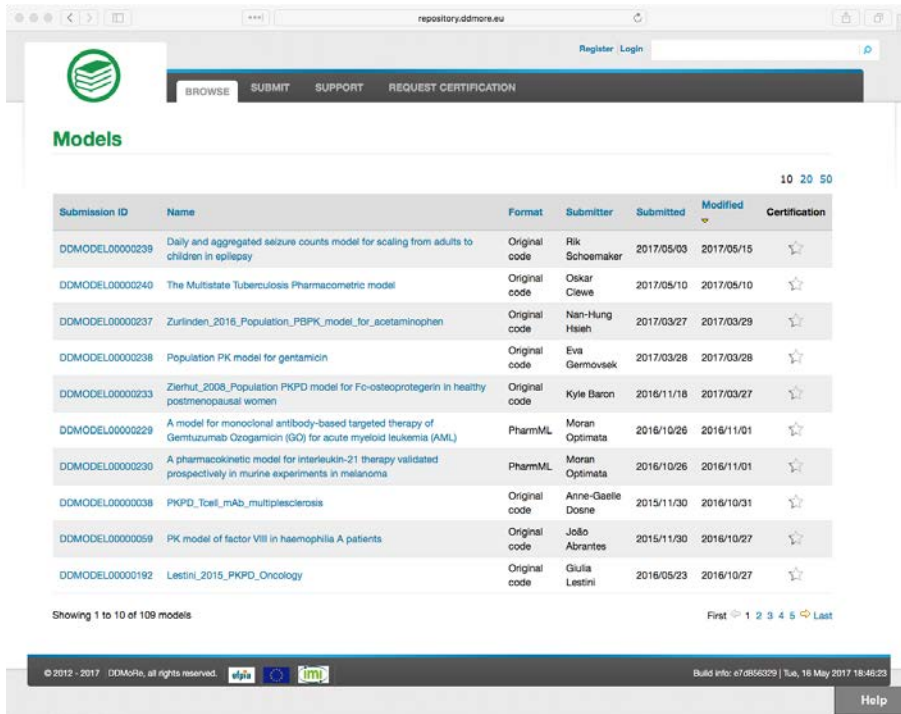# DDMoRe Consortium: Interoperability Framework

- Converters are available for many important software tools

- Converters can be used outside IOF or within Integrated Development Environment (IDE)

Converter	Implementation Language	Platform
MDL->PharmML	Java	All
PharmML-> NMTRAN	Java	All
PharmML->MLXTRAN	C++	Windows, Linux
PharmML-> WinBUGS	Java	All
PharmML-> PFim	Java	All
PharmML->PopED	C++	All
NONMEM->SO	Perl (PsN)	All
Monolix->SO	C++	All
WinBUGS->SO	Java	All
Pfim->SO	Java	All

DDMoRe Consortium: Model Repository

- Developed software to host model repository

- Curated and published ~100 models
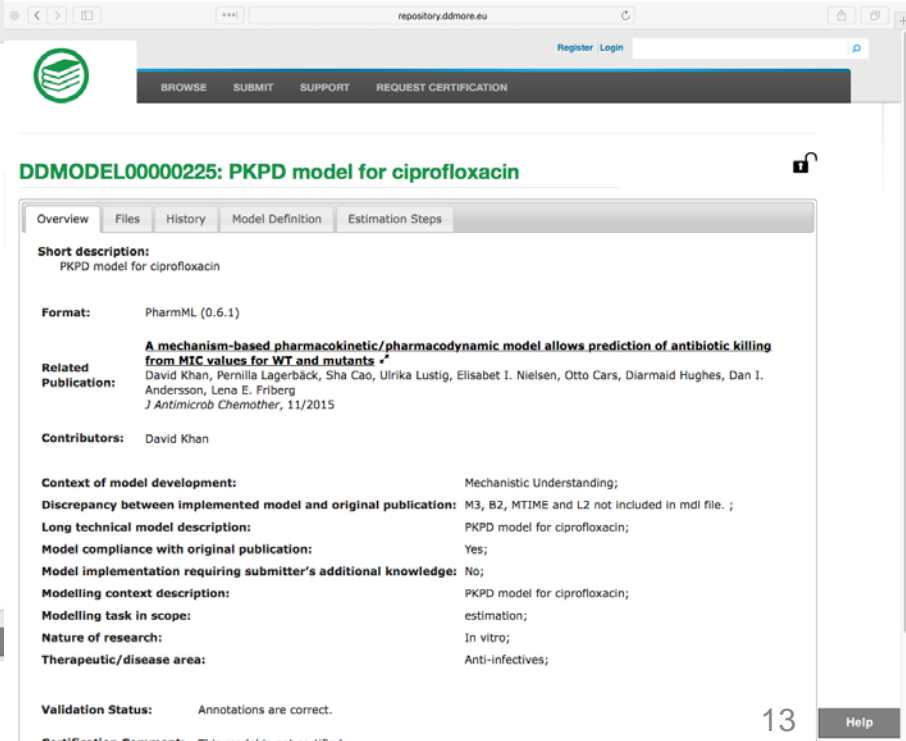
- Repository hosted and publicly available.

Alignment between the EFPIA MID3 Good Practice and DDMoRe

WHITE PAPER

Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation

EFPIA MID3 Workgroup: SF Marshall[1]*, R Burghaus[2], V Cosson[3], SYA Cheung[4], M Chenel[5], O DellaPasqua[6], N Frey[3], B Hamrén[7], L Harnisch[1], F Ivanow[8], T Kerbusch[9], J Lippert[2], PA Milligan[1], S Rohou[10], A Staab[11], JL Steimer[12], C Tornøe[13] and SAG Visser[14]

Good Modelling Practices

"Quantitative framework for prediction and extrapolation, centered on knowledge and inference generated from integrated models of compound, mechanism and disease level data and aimed at improving the quality, efficiency and cost effectiveness of decision making''

Alignment between FDA PDUFA VI MIDD Initiative and DDMoRe

- MIDD Description
  - "…development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources…"
- FDA will convene a series of workshops to identify best practices for MIDD. Workshop topics will include:
  - Physiologically-based pharmacokinetic modeling
  - Design analysis and inferences from dose-exposure-response studies
  - Disease progression model development, including natural history and trial simulation
  - Immunogenicity and correlates of protection for evaluating biological products, including vaccines and blood products
- Each workshop will focus on current and emerging scientific approaches, including methodological limitations

- Who we are

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DDMoRe Foundation Objective

The DDMoRe Foundation will foster******* the advancement of methods and greater efficiency in the practice of MIDD/MID3 and drug usage**

* Through Advocating, Facilitating, Supporting and Provision

DDMoRe Foundation Objectives

Advocating

Galvanize the quantitative community towards standards and integration

Increase transparency in the model building process and associated assumptions

Offer and actively pursue efficient knowledge integration

Facilitating

Facilitate advances towards an interconnected community

Maintain and enhance the public domain content from the DDMoRe Consortium

Maintain and develop exchange standards

Supporting

Increase DDMoRe platform utilization and global awareness

Improve efficiency and quality in model building and application

Support the community with public domain standards and tools

Providing

Provide specific DDMoRe Foundation Partner benefits

Ensure access to high quality drug and disease models

Expand DDMoRe platform capabilities according to the wishes of the DDMoRe Foundation Partners

INDUSTRY
REGULATORS
JOURNALS
DRUG DEVELOPMENT
UNIVERSITIES
VENDORS
PAYERS
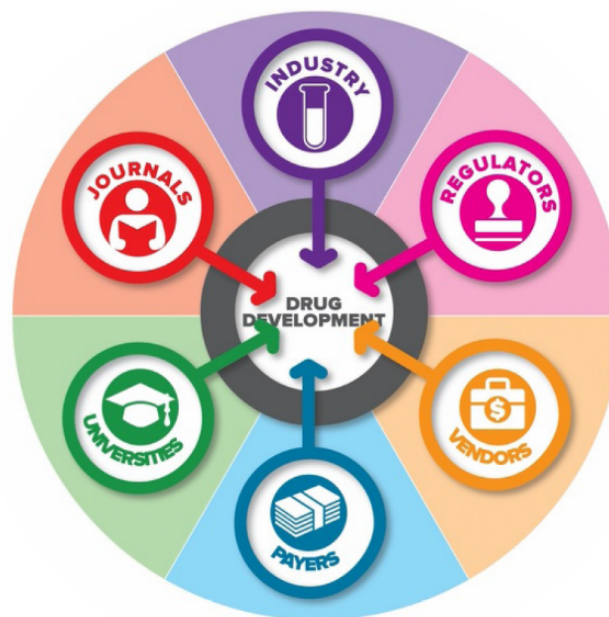
DDMoRe Foundation Design Principles

Sustainable	Able to sustain the DDMoRe Consortium infrastructure for the benefit of the quantitative community for a long period of time
Not competitive	Not a competitor for commercial suppliers in the quantitative community, but seeding competition to improve tools for the quantitative community
Independent	Autonomous, not relying on the financing or viewpoint of a single company/academic institution
Representative	For all types of participants in the quantitative community
Easily accessible	Organizations can easily join and make use of the exchange standards
Financially viable	Able to generate sufficient revenue to cover costs
Efficient	"Lean and mean" organization; able to take decisions
Not for profit	Reinvesting income in maintaining/improving infrastructure for the community
Adaptive	Able to benefit from and operate in a changing environment

Level of Practice Integration Across the Quantitative Community*

Today

- A Quantitative Community of parts

- Largely unstructured exchange channels across discrete parts, and the community as a whole
  - Greater community integration is not a priority
  - Greater community consistency of practice is not a priority
  - Greater community level influence is not a priority

Tomorrow

An interconnected Quantitative Community

Largely structured exchange channels across discrete parts, and the community as a whole

Greater community integration is a priority

Greater community consistency of practice is a priority

Greater community level influence is a priority

*Quantitative community: Academia, Regulatory, Industry, CROs, Software Vendors etc.

Future Level of Practice Integration Across the Quantitative Community
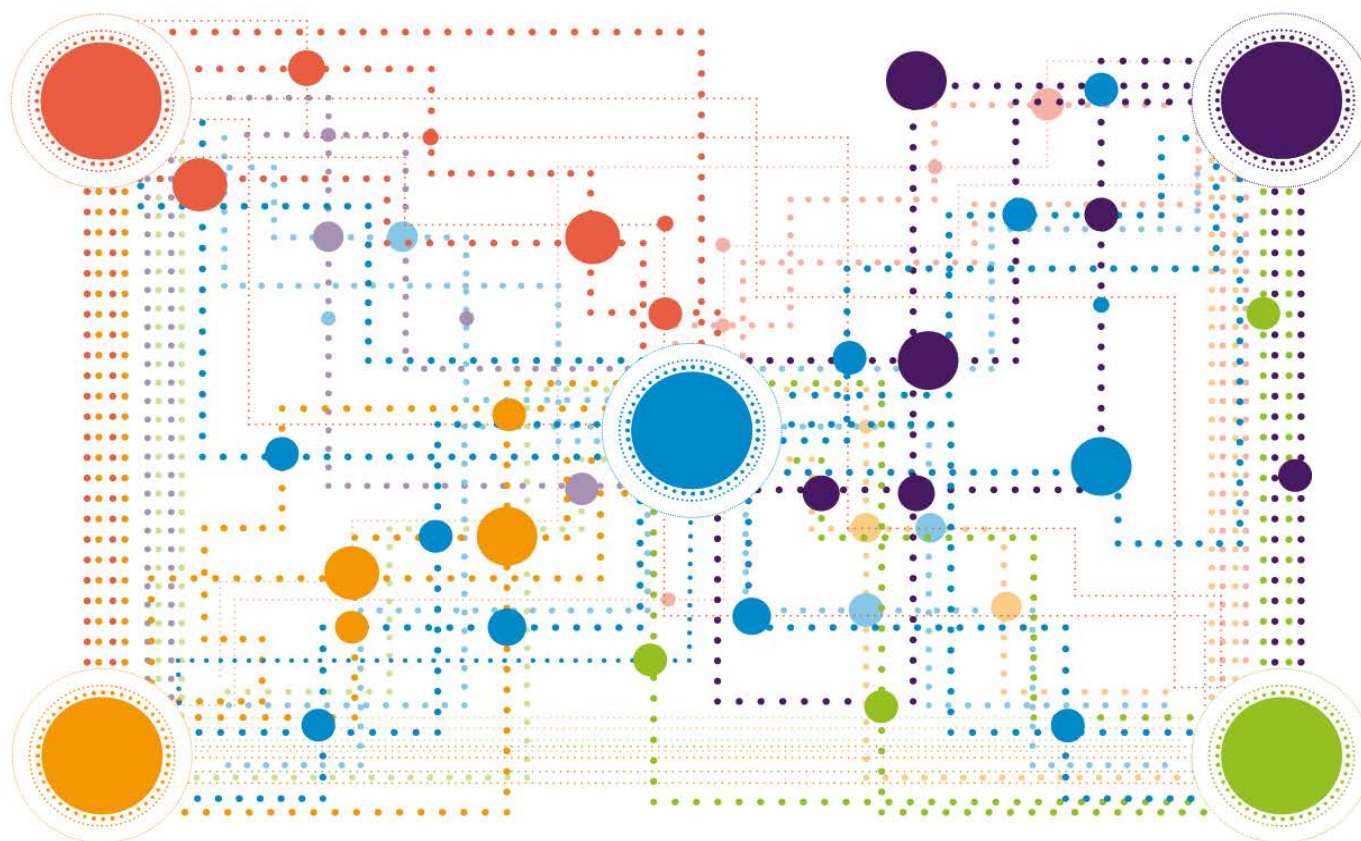
Academia   Regulatory   Industry   CRO's   Software/Tools

- Who we are

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What have we done (since September 2016)
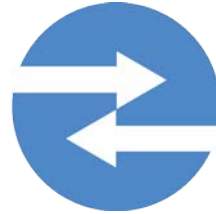
Model Repository   Standards   Thoughtflow
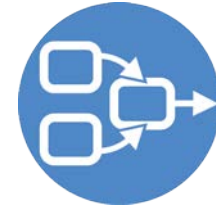
Community groups

23
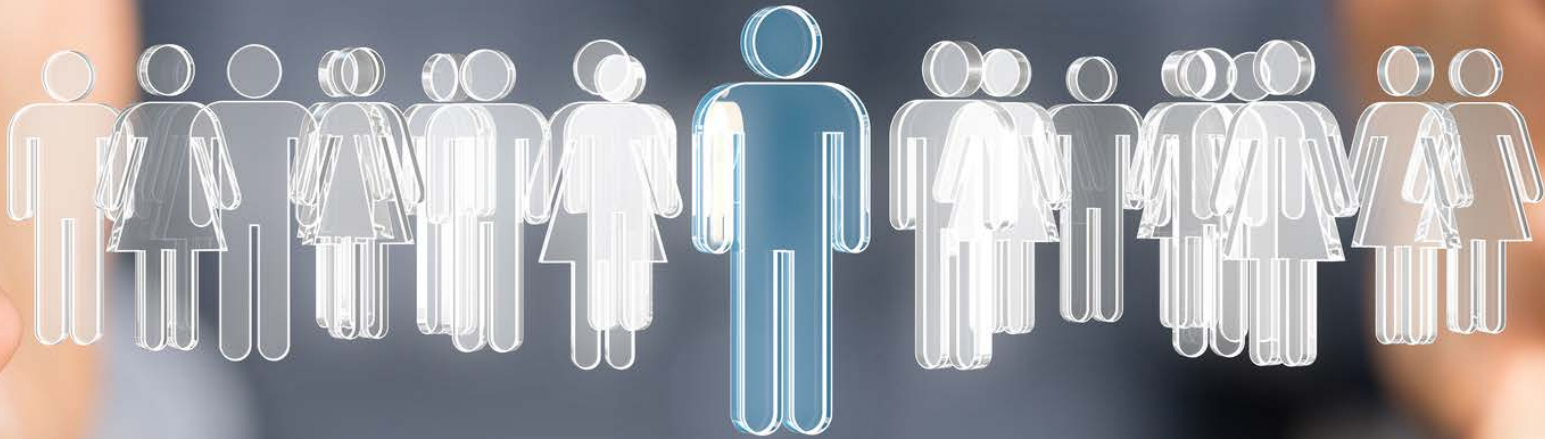
DDMoRe Foundation Outreach

- Community groups have been established

  - Community group profiles have been installed

  - First community challenge has been launched

- Advisory group establishment initiated

  - Regulatory group dialogue ongoing

  - Software developer dialogue ongoing

- Letters of support provided for 2 tuberculosis consortia

  - IMPLICATED: "In-silico trails for developing and assessing biomedical products"

  - SUPPORT: "Personalized computer models and in-silico systems for well being"

- Online training has been internalized, harmonized and is provided on the DDMoRe Foundation website

- Website, LinkedIn and twitter has been updated and update communication strategy developed

What have we done

PharmML 0.8.1
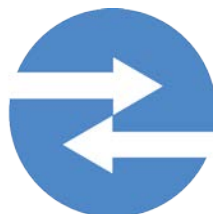
Exchange
Standards

Model Repository

Interoperability

Languages

- DDMoRe Foundation contributions:

- Website: www.mdl.community
  - Contribute via GitHub
- MDL User Guide now online
  - https://modeldefinitionlanguage.github.io/MDLUserGuide/
- MDL-Editor for Windows, Mac OSX, Linux
  - http://downloads.mdl.community/repository/mdl-ide/products/1.6.0/

Languages

- Community group contributions:

- 3 meetings
  - 22nd Feb, 29th March, 8th June
- Sub-team set up to take DDMoRe Language standards (MDL, PharmML, SO and ancillary tools like libpharmml) to "Production" status.
  - Production versions will be supported and maintained by DDMoRe Foundation.
  - Development versions will be used to define, test new features.
- Paolo Magni's group has presented a poster using and extending the DDMoRe standards, at PAGE 2017: "Execution of complex Bayesian workflows with the DDMoRe Interoperability Framework: a case study in the diabetes area". https://www.page-meeting.org/default.asp?abstract=7188

Model Repository

- DDMoRe Foundation Contribution:

- Now hosted and managed by the Foundation

- New version of repository software features:

  - Stability bug fixes

  - Rendering of PharmML 0.8.1 – compatible with interoperability tools.

  - User interface improvements

Model Repository

- Community Group Contributions:

  - Established February 2017, so far 4 meetings with >15 people

  - Demo to all members on how to submit a model, description of model certification

  - Tasks done: Welcoming package for new members (on website)

  - Active Tasks:

    - DDMoRe model repository sponsorship/challenge

    - Paper selection from literature for model code upload (started with CPT:PSP and JPKPD)

    - List of convincing arguments for model sharing

    - Check compliance of submitted model entries with submission guidelines

    - Model repository test

Thoughtflow

- DDMoRe Foundation Contribution:

  - Completion of DDMoRe Consortium deliverable with publication of the PROV-O standards in a white paper:

  [Thoughtflow: Standards and Tools for Provenance Capture and Workflow Definition to Support Model Informed Drug Discovery and Development](#)

- Community Group Contribution:

  - Established February 2017

  - We have a website: http://thoughtflow.community/

  - There's a demo: http://tfserver.ddmore.foundation:8080/bwf/

  - There's a video: https://www.scinteco.com/index.php/2016/09/18/ddmore-workpackage-thoughtflow/

  - The group has met a number of times to review the standards, and to explore the demonstration site

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What we would like to do

PharmML 0.8.1

Exchange
Standards

Model Repository   Thoughtflow   Interoperability
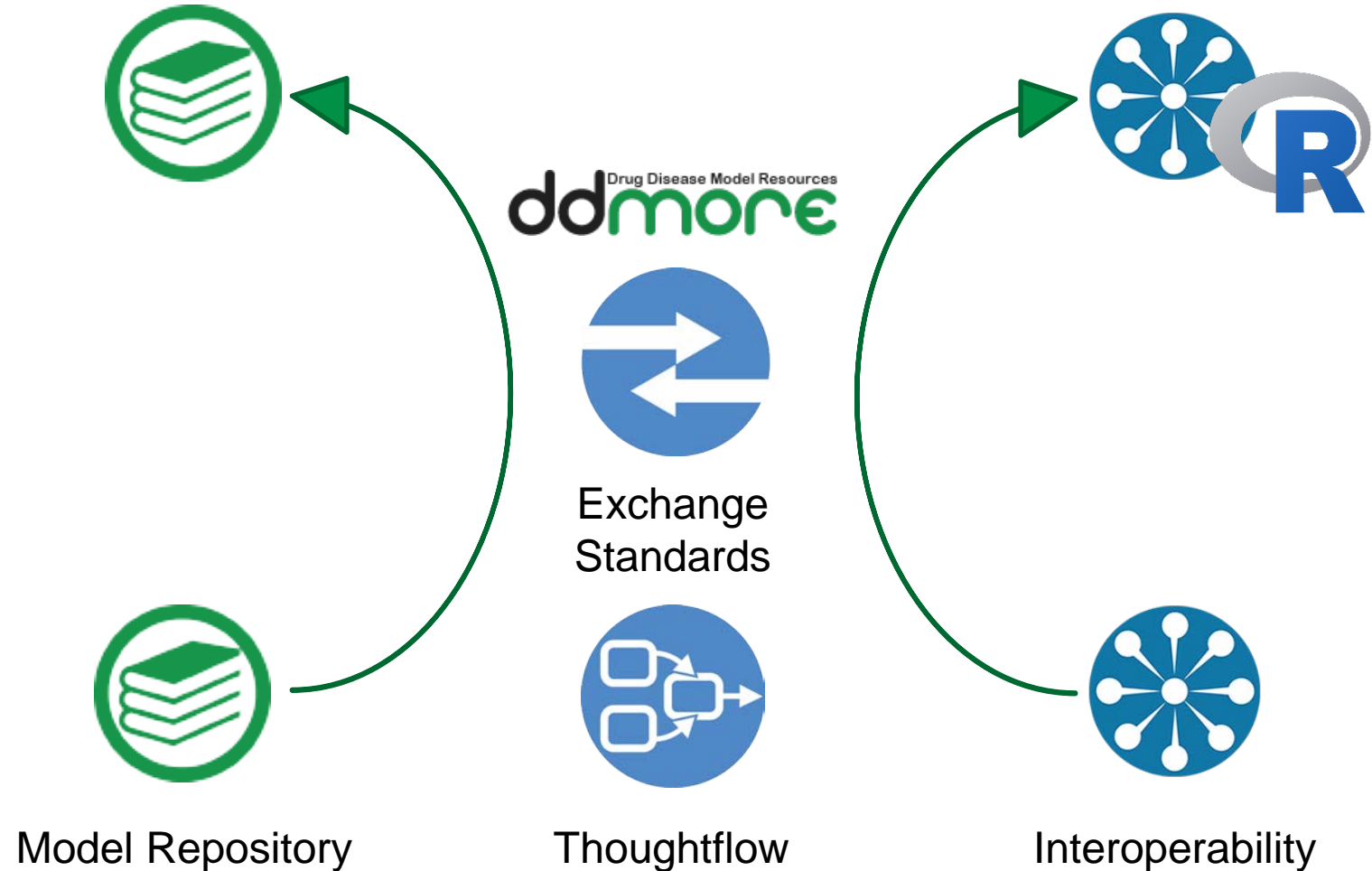
Languages

- v1.0 "Production" release of PharmML, SO, libPharmML, libSO, etc.

- Define the process for defining, discussing, documenting new language features and their implementation.

  - Aim to release new language features into production following testing in development versions.

  - Will implement features across languages so that standards move forward together.

- Need to extend MDL to cover additional model features and ensure that MDL -> PharmML conversion is solid for these.

  - E.g. BLQ handling; within-sample models i.e. L2; extend error model specification etc.

Model Repository

- Future

  - Upgrade all PharmML models to 0.8.1

  - Further user interface improvements including "fast track" process

  - Private instance of repository refinement

  - Scientific Meeting and Society partnership

  - Further capability improvements including "data"

Thoughtflow

- We need to update a blueprint for a free, open-source tool to serve the needs of all of our potential users

- We need a working implementation
  - Based as heavily as possible on and around R

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- **How can you help**

How Can You Help: Pharmaceutical Companies

- Promote greater utilization and adoption of public domain DDMoRe Platform content within your organization

  - DDMoRe Repository, Interoperability Framework, Exchange Standards

- Become a DDMoRe Foundation Partner and receive Partner Specific Benefits such as:

  - A private version of the DDMoRe Repository, which enables the sharing of proprietary drug and disease models and their related content (including proprietary data) within an organization.

  - An alternative version of interoperability framework compatible with distributed environments and infrastructure within their organization

  - Customized training and support which can be provided as in-house "hands-on" offerings. In addition the DDMoRe Foundation will provide its Partners access to subject matter experts who can provide guidance and coaching on DDMoRe exchange standards, repository and tools.

  - Ability to influence DDMoRe Foundation strategies for the short, medium and long term

- Financially support the not for profit DDMoRe Foundation

  - *Help us to Help you – please contact Marylore Chenel, Peter Milligan*

How Can You Help: Universities

- Promote greater utilization and adoption of public domain DDMoRe Platform content within your organization

    - DDMoRe Repository, Interoperability Framework, Exchange Standards

- Become a DDMoRe Foundation Partner and receive Partner Specific Benefits such as:

    - Receive assistance in the development of methodologies and/or tools through testing and implementation.
        - Access to Foundations software support resources (see later slide).

    - Receive DDMoRe Foundation accreditation for service/tool provision to a specific DDMoRe standard.

    - Access to subject matter experts who can provide guidance and coaching on DDMoRe exchange standards, repository and tools.

    - Ability to influence DDMoRe Foundation strategies for the short, medium and long term

    - DDMoRe supported/sponsored research to be pursued and for the DDMoRe Foundation itself, to seek support for external funding bodies.

- Contribute in kind support for the not for profit DDMoRe Foundation

    - *Help us to Help you – please contact Mats Karlsson, Paolo Magni*

How Can You Help: Regulatory Agencies

- Promote greater utilization and adoption of public domain DDMoRe Platform content within your organization

    - DDMoRe Repository, Interoperability Framework, Exchange Standards

- Become a DDMoRe Foundation Partner and receive Partner Specific Benefits such as:

    - A private version of the DDMoRe Repository, which enables the sharing of proprietary drug and disease models and their related content (including proprietary data) within an organization.

    - An alternative version of interoperability framework compatible with distributed environments and infrastructure within their organization

    - Customized training and support which can be provided as in-house "hands-on" offerings. In addition the DDMoRe Foundation will provide its Partners access to subject matter experts who can provide guidance and coaching on DDMoRe exchange standards, repository and tools.

    - Ability to influence DDMoRe Foundation strategies for the short, medium and long term

- Contribute in kind/financial support for the not for profit DDMoRe Foundation

    - *Help us to Help you – please contact Marylore Chenel, Mats Karlsson, Paolo Magni, Peter Milligan*

How Can You Help: Scientific Bodies and Journals

- Promote greater utilization and adoption of public domain DDMoRe Platform content within your organization

  - DDMoRe Repository, Interoperability Framework, Exchange Standards

- Become a DDMoRe Foundation Partner and receive Partner Specific Benefits such as:

  - An alternative version of the DDMoRe Repository, which enables the sharing of drug and disease models and their related content within an organization.
    - Promote peer review of submitted manuscripts and their associated model code
    - Promote sharing and reuse of model code from accepted for publication manuscripts
    - Promote sharing and reuse of model code from accepted abstracts and presentations from scientific meetings
  - Ability to influence DDMoRe Foundation strategies for the short, medium and long term

- Contribute in kind/financial support the not for profit DDMoRe Foundation

  - *Help us to Help you - please contact Marylore Chenel, Mats Karlsson, Paolo Magni, Peter Milligan*

How Can You Help: CROs

- Promote greater utilization and adoption of public domain DDMoRe Platform content within your organization
    - DDMoRe Repository, Interoperability Framework, Exchange Standards

- Become a DDMoRe Foundation Partner and receive Partner Specific Benefits such as:
    - A private version of the DDMoRe Repository, which enables the sharing of proprietary drug and disease models and their related content (including proprietary data) within an organization.
    - An alternative version of interoperability framework compatible with distributed environments and infrastructure within their organization
    - Receive DDMoRe Foundation accreditation for service/tool provision to a specific DDMoRe standard.
    - Access to subject matter experts who can provide guidance and coaching on DDMoRe exchange standards, repository and tools.
    - Ability to influence DDMoRe Foundation strategies for the short, medium and long term

- Financially support the not for profit DDMoRe Foundation
    - *Help us to Help you - please contact Marylore Chenel, Mats Karlsson, Paolo Magni, Peter Milligan*

How Can You Help: Software Developers/Vendors

- Promote greater utilization and adoption of public domain DDMoRe Platform content within your organization
    - DDMoRe Repository, Interoperability Framework, Exchange Standards
    - Maintain and/or develop tool specific converter/connectors to the interoperability framework
- Become a DDMoRe Foundation Partner and receive Partner Specific Benefits such as:
    - Receive assistance in the development of methodologies and/or tools through testing and implementation.
        - Access to Foundations software support resources (see next slide).
    - Receive DDMoRe Foundation accreditation for service/tool provision to a specific DDMoRe standard.
    - Access to subject matter experts who can provide guidance and coaching on DDMoRe exchange standards, repository and tools.
    - Ability to influence DDMoRe Foundation strategies for the short, medium and long term
- Contribute in kind/financial support the not for profit DDMoRe Foundation
    - ***Help us to Help you - please contact Marylore Chenel, Mats Karlsson, Paolo Magni, Peter Milligan***

Software Developer/Vendor Support Resources

- DDMoRe Foundation can provide its partners with the following:

  - Access to prebuilt binaries of all DDMoRe libraries and products

    - Only source code available to non-partners

  - Access to latest development binaries

  - Access to Foundation's Artifactory server

    - A single repository to access all DDMoRe libraries and their dependencies.

    - Guarantees you have access to all dependencies needed to develop DDMoRe related tools.

  - Prioritisation of bug fixes and enhancements as needed by Foundation Partners

How Can You Help: Individuals

- Promote greater utilization and adoption of public domain DDMoRe Platform content within your organization

    - DDMoRe Repository, Interoperability Framework, Exchange Standards

- Become a DDMoRe Community Group member and:

    - Contribute to and influence DDMoRe Foundation strategy and implementation for the short, medium and long term

    - Gain access to early development releases

    - Exchange and share

    - Become a role model for the quantitative community

- Contribute in kind support for the not for profit DDMoRe Foundation

    - *Help us to Help you – please contact Celine Sarr, Mike K Smith, Justin Wilkins*

Contact Us

For more information, comments or questions on the DDMoRe Foundation please contact:

Board Members:

- Marylore Chenel – Servier
  - marylore.chenel@ddmore.foundation
- Mats Karlsson - University of Uppsala
  - mats.karlsson@ddmore.foundation
- Paolo Magni - University of Pavia
  - paolo.Magni@ddmore.foundation
- Peter Milligan – Pfizer
  - peter.milligan@ddmore.foundation

Technical and Management support:

- Wendy Aartsen - Hands4Grants
  - wendy.aartsen@ddmore.foundation
- Stuart Moodie – Eight Pillars
  - stuart.moodie@ddmore.foundation