Fractionated Plasma Products

Business as usual ? – or what?

Experience with 5 years revised EU Pharmacovigilance Legislation

Biotest AG

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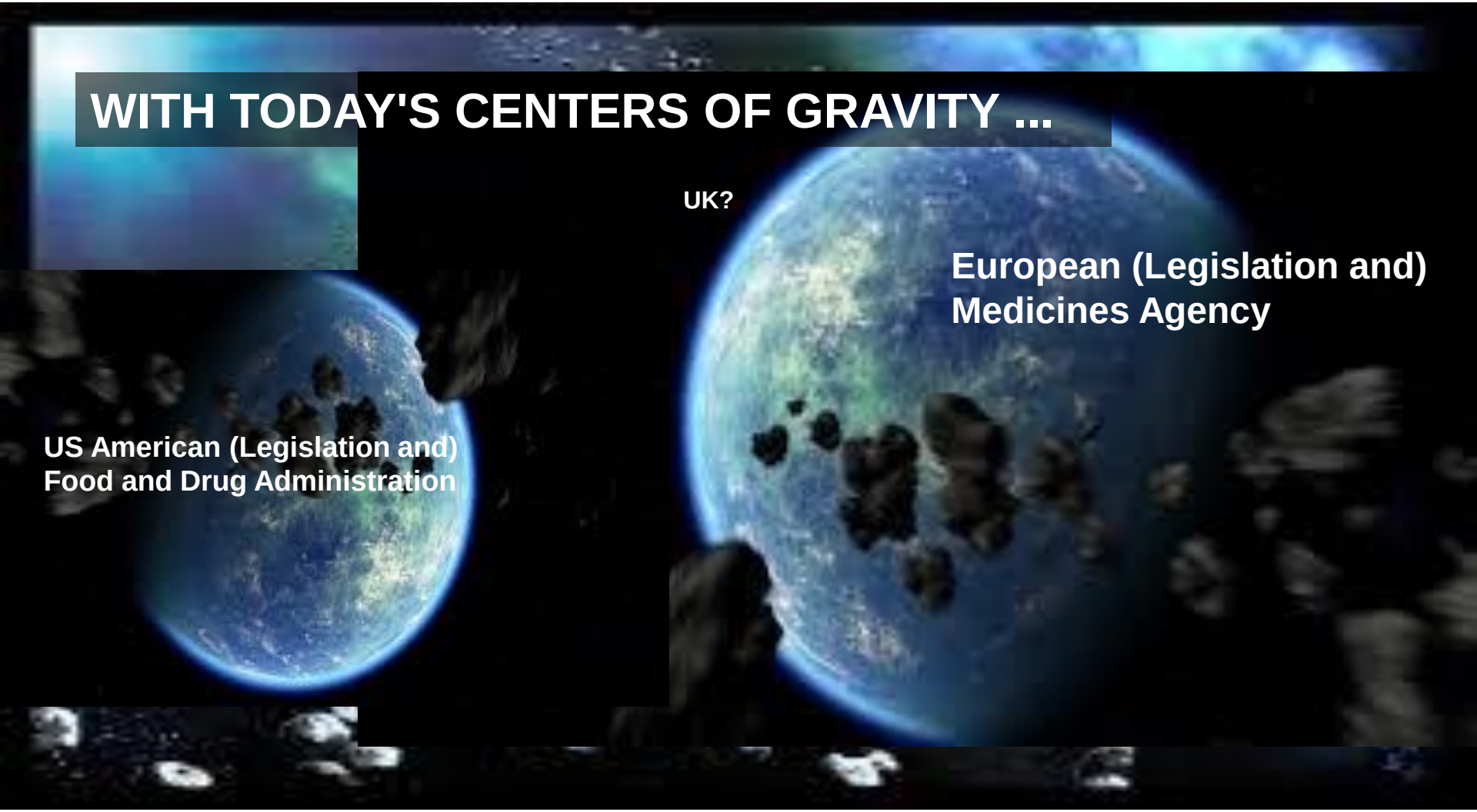
EU QPPV and Head Corporate Drug Safety

Well – plasma related specifics have not changed much compared to the situation "before the big change"

- Donor specification
- Biological Variability
- Transmission of infectious diseases
- batch related ww traceability of sold end-products
- Lookback
- Specific batch release
- polymer and aggregation
- Transport, storage and handling error
- immunogenicity,
- Lack of efficacy

what has changed is Pharmacovigilance as a "System"



Regulatory framework EU

- Dir 2001/83 as revised 2010 by Dir 2010/84: Safety Harmonisation CAP, NAP, MRP, including Plasma-derived Medicinal Products

  TITLE IX (Pharmacovigilance)
  TITLE X (Blood)
  TITLE XI (Supervision and Sanctions)

- Dir 2002/98 amending 2001/83 with respect to whole blood and plasma: Hemovigilance
- Dir 2012/26 amending 2001/83 in aspects Pharmacovigilance
- Reg 726/2004 as amended
- Reg 1235/2010: Safety Harmonisation parallell to Dir 2010/84
- Reg 520/12: Implementing Regulation: Safety Harmonisation
- GVP Modules: Legal binding guidance regarding central aspects of a MAH PV System and Processes

"Whole" versus "Fractionated"

Whole Blood/Components Transfusion/-plantation:

- **Red Blood Cell Transfusions**
- **Plasma Transfusions**
- **other**

excluded from 2001/83
⇒Dir 2002/98 EC
⇒Amendment 2001/83

Fractionated Blood/Plasma : <u>Pharmacotherapy</u>

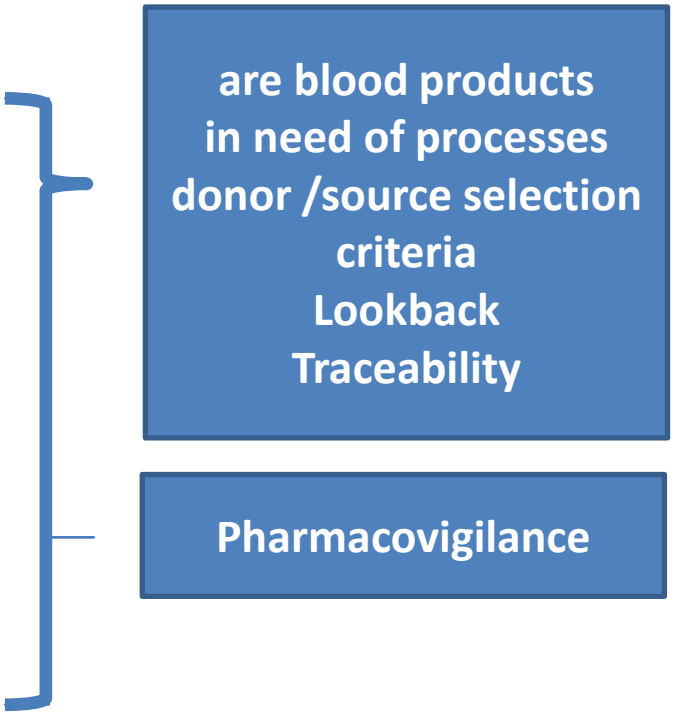
- **Polyclonal Immunoglobulins**
- **Factor VIII/IX preparations**
- **Fibrinogen**
- **other**

Pharmacovigilance 2001/83 EC

"Fractionated": Pharmacotherapy but nevertheless "Blood Products" all addressed by Dir 2001/83

Blood/Plasma fractionation: <u>Pharmacotherapy</u>

- **Polyclonal Immunoglobulins**
- **Factor VIII/IX preparations**
- **Fibrinogen**
- **other**



2001/83 and 2002/98

The establishment of high standards of quality and safety, therefore, will help to reassure the public that human blood and blood components which are derived from donations in another Member State nonetheless meet the same requirements as those in their own country.

2001/83 Title X

SPECIAL PROVISIONS ON MEDICINAL PRODUCTS DERIVED FROM HUMAN BLOOD AND PLASMA

Article 109

For the collection and testing of human blood and human plasma, Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC (1) shall apply.

Article 110

Member States shall take the necessary measures to promote Community self-sufficiency in human blood or human plasma. For this purpose, they shall encourage the voluntary unpaid donation of blood and plasma and shall take the necessary measures to develop the production and use of products derived from human blood or human plasma coming from voluntary unpaid donations. They shall notify the Commission of such measures.

2001/83 Title XI Supervision and Sanctions

Article 115

Member States shall take all necessary measures to ensure that the manufacturing and purifying processes used in the preparation of medicinal products derived from human blood or human plasma are properly validated, attain batch-to-batch consistency and guarantee, insofar as the state of technology permits, the absence of specific viral contamination. To this end manufacturers shall notify the competent authorities of the method used to reduce or eliminate pathogenic viruses liable to be transmitted by medicinal products derived from human blood or human plasma. The competent authority may submit samples of the bulk and/or the medicinal product for testing by a State laboratory or a laboratory designated for that purpose, either during the examination of the application pursuant to Article 19, or after a marketing authorization has been granted.

2002/98/EC

In respect of blood or blood components as a starting material for the manufacture of proprietary medicinal products, Directive 2001/83/EC refers to measures to be taken by Member States to prevent the transmission of infectious diseases ..... as regards in particular the selection and testing of blood and plasma donors.

Now, the not so new anymore ...
EU Pharmacovigilance "Revolution" ....

Biotest
From Nature for Life

... harmonised international, but increased detail,

since 2012, ~ 380 pages

- I: PV Systems and their Q Systems
- II: Pharmacovigilance System Master File
- III: PV Inspections
- IV: PV Audits
- V: Risk Management Systems (-Plans)
- VI: Adverse Reaction Reporting
- VII: Periodic Safety Update Reports
- VIII: Post-Authorisation Safety Studies
- IX Signal Management
- X: Additional Monitoring
- XV: Safety Communication
- XVI: Risk Minimization Measures including Educational Material

up to 2012 Volume 9A parts I, IV,

~ 135 pages

PVS and its QS : GVP I

Sounds like "Rules Ruling Rules"

None, but now they work together

Don't worry – QA in PV - it's just bit ...

- Writing
  - SOP (QPPV, PSMF, Signal Handling/Safety Labeling, RMP, PSUR, ICSR, Crisis Decision Management, Action Plan a.s.o.)
  - Contractual Agreements "Safety Data Exchange"
- Defining
  - KPI
  - and a CAPA process
  - that better be kept, otherwise getting an "on cause"
- Audit
  - Audit Plan
  - Conducted by a QA Specialist not member of the PV group
  - PV group assignes subject matte expert
- Investment in budget (external) and/or resources (internal)

PVQA: often negelcted but considered a V.I.P.rocess

- Proper Drug Safety Exchange (or Contractual Safety) Agreements
  - relevant functions with contact details, even names
  - listing products
  - describing in detaíl processes re signaling, labeling, crisiis, reporting and defining delineations in responsiibility
  - in detail quality KPI
  - audit intervals

GVP I and II, what else ... established a worksharing PV responsibility between MAH (Management Board) and QPPV

in between would be a Head of PV

surrounded by local Drug Safety Responsibles at Affilated Companies and Partners

... addresses Duties of the MAH

- Continuous monitoring of PV data including examination of options for risk minimisation
- Robust interface PVS and product quality defect system
- Robust interface PVS and labeling implementation system keeping product information up to date
- Emergency issue management concept and communication process about safety concerns
- Establish Business Continuity Plans / IT Disaster Recovery / Epidemic Emergency

in doing so, supporting the QPPV

.... MAH continued

- Provide adequate support with:
  - **appropriate resources (number, expertise) available**
  - **appropriate processes (standard, measurable) in place**
  - **early notification on acquisitions, be it a product or a company**
  - **any information with possible impact on the risk-benefit-balance, e.g. from sponsored or unsponsored studies, registries, partners**
- Attribute sufficient authority with
  - **influence the performance of PVS, QS and ongoing/completed CTs**
  - **impact regarding preparation of RMPs and regulatory action (variations, USRs, safety communication)**
- Provide access to all sources of relevant information (e.g. database)

... motivates the MAH to ensure

- ... the QPPV has acquired **adequate theoretical and practical knowledge** for the performance of pharmacovigilance activities. The QPPV should have **skills for the management of PV systems** as well as expertise or access to expertise in relevant areas such as **medicine, pharmaceutical sciences as well as epidemiology and biostatistics**.
- If the QPPV has not completed basic medical training …, **access to a medically trained person** shall be available and this access should be documented in the PSMF.
- The expectation is that the **MAH will assess the qualification of the QPPV** prior to appointment by, for example, reviewing university qualifications, knowledge of EU PV requirements and experience in pharmacovigilance.
- The applicant or MAH **should provide the QPPV with training** in relation to its PV system, which is appropriate for the role prior to the QPPV taking up the position and which is appropriately documented.

... defines QPPV duties

... like

- Shall be at the MAH's disposal **permanently & continuously**
- Shall reside and operate in the EEA.
- Back-up **person** should be in place
- **Responsible** for the maintenance PV system and the PSMF.
- Having an overview of medicinal **product safety profiles** and any **emerging safety concerns**
- Having awareness of any post-authorisation **(safety) commitments**
- Having awareness of **any risk minimization measures**
- Being involved in the review of **PASS protocols**
- Providing input into **risk management plans**
- Ensuring submission of all PV-related documents

... and more

- Ensuring necessary **quality, including the correctness and completeness, of PVdata submitted** to the competent authorities (CA) of Members States and the Agency
- Ensuring a **full and prompt response** to any request from the competent authorities
- Providing input into the preparation of **regulatory action** in response to emerging safety concerns (e.g. variations, urgent **union procedures** *(Anm. former urgent safety restrictions),* **and communication to patients and healthcare professionals**)
- Acting as a **single pharmacovigilance contact point** for the CAs and the Agency **on a 24-hour basis** and also as a **contact point for pharmacovigilance inspections.**

... and

- QPPV has oversight over the functioning of the system **in all relevant aspects**, including its quality system (e.g. SOPs, contractual arrangements, database operations, compliance data regarding e.g. quality and ICSR exchange, completeness and timeliness of expedited reporting and submission of periodic update reports, audit reports and training of personnel in relation to pharmacovigilance).
- QPPV should be aware of **the validation status of the database**, including any failures that occurred during validation and the corrective actions that have been taken to address the failures.
- QPPV should also be informed of **significant changes that are made to the database**.

.. in the end – the QPPV is a kind of ...

Some relief provided in GVP section I.C.1.3.:

The QPPV **may delegate specific tasks, under supervision**, to appropriately qualified and trained individuals, for example, acting as safety experts for certain products, provided that the QPPV maintains system oversight and overview of the safety profiles of all products. Such delegation should be documented."

last but not least – QPPV – whats not exactly in the law but important to determine at company level

- **QPPV has oversight over the functioning of the system in all relevant aspects,** ... but
  - what if there is a "Global" PV System ?
  - a "Global" Head of Pharmacovigilance ?
  - a Headquarter based outside Europe ?
- **Legislation defines a lot of responsibility and even functional reporting line of local (EU-based?) QPPV, ... but**
  - where should an EU QPPV report to ?
  - for what reasons ?
  - Where should an EU QPPV not report to ?
  - for what reasons ?

... solutions

- There is no "exact" solution ... many are possible and acceptable depending company size and organisation
- Essential is, that a QPPV can offer **"A"** solution with a reasonable justification ....
- The Global context must support EU legislation, even adopt it as "Global" if it is "most strict".
- **Solutions are going to be validated at**
  - **GVP System inspection**
  - **GVP System audits**

No – the real last but not least thing in the PV Revolution is the Pharmacovigilance System Master File (PSMF)

PSMF = An EU Standard of the Documentation of an MAH's PV System

From DDPVS to PSMF

~ 1990: "Detailed Description of the PV System" as part of every submission dossier

resulted in Dossiers with different versions of DDPVS depending on submission date

constantly updated but stationary 2012 PV System "MASTER" File

Dossiers only with a VERY light but stable "summary" version of the PSMF

PSMF contents

- **Company Organisational Chart(s) incl. position of QPPV**
- **Qualified Person responsible for Pharmacovigilance**
- **Job Descriptions**
- **Products Lists**
- **Organisation (units, subunits, activities, flow diagrams)**
- **Procedures documented in writing (GOPs / SOPs / WIs)**
- **Number of PSMFs and/or name(s) of MAHs sharing the PSMF if applicable**

on request, MAH to provide an validated update within 7 Calendar days

... more contents

- Database/s (relevant for Pharmacovigilance)
- Links with other Organisations
- Log-Book
- Documentation & Archiving
- Quality Management (of the PVS)
  - Training
  - Auditing
- Signal Management
- Risk Management
- Version and Version Control

on request, MAH to provide an validated update within 7 Calendar days

Two more slides on GVP VI and IX

GVP VI: Adverse Reaction Reporting

- Good
  - harmonized across the EU
  - irrespective of CAP, NAP, MRP
- Not so ...
  - member states still want their specials
  - implementation at different levels
  - non-serious cases to be reported
  - costly new database configuration (ICH E2B (Rev3) at the horizon
  - GVP Module very complex and lengthy

GVP IX: Signal Management

- Good
  - a formalised process
  - irrespective of CAP, NAP, MRP
  - once understood generates good plausibility
- Not so ...
  - a TOOO formalised process
  - and difficult to interpret
  - particular in the decision, when is it still a "case" and when does it start as a "signal"
  - GVP Module very complex and lengthy

  - As mentioned previously: Investment needed ....

now back to plasma-derived Medicinal Products

even more challenging

wait a moment ...

The interface GMP Quality and GVP Safety

- Must be "robust" – particularly with plasma proteins, means
  - clear delineation of roles and responsibilities – who does what when (SOP/WP)
- GMP: When to involve GVP?
- GVP: when to involve GMP?

To bring on board supervisory authority ...

- In case of potential RAS II or even I: better earlier
- In case of processing product complaints: An important customer need, an important source of risk signal, company should know that this is important: So
  - Proposed are categories that define timelines for processing
  - making it an auditable KPI
- Last but not least: Consider PV Database to be the home of PTC?
- Otherwise cost are doubled.

now back to plasma-derived Medicinal Products

even more challenging

Organisational aspects "Plasma" in the new PV Legislation

- Authorities: build contacts; War Talks in Peace Times
- Safety should know their prescribers, KOL
  - Who could support in crisis issues?
  - who could be consulted per issue?
  - on ww level?
- Interfaces internally:
  - Toxicology
  - Sourcing
  - GMP (Manufacturing, QC, QA, QP)
  - Sales/Distribution/Affiliates: Get knowledgeable around local specifics in critical areas: Transmission infective agents, distribution (direct to patients?), Recall RAS I (what to do?)
- Medical Expertise: Clinical Immunology, Pediatrics, Internal Med
- Scientific Expertise: Biochemistry

Still relevant with Plasma – as with any Bio Product

- Higher expectations and standards in SAFETY (not necessarily PV)
- Lower risk tolerance
- delayed risks
- Evaluation of rarest risks
- all ingredients can cause side effects
- use of the "precautionary principle" (e.g. TSE)
- Risk communication very sensitive (TSE, HIV etc)
- safety related effects of slightest changes in manufacturing

Still relevant with Plasma – as with any Bio Product

Compared to small molecules – more and detailed information should be available regarding:

- Source Material
- Manufacturing Process
- Changes in the Manufacturing Process
- Additives
- Off label use
- International: Prescription behaviour
- Recall process

- Pro-active QC

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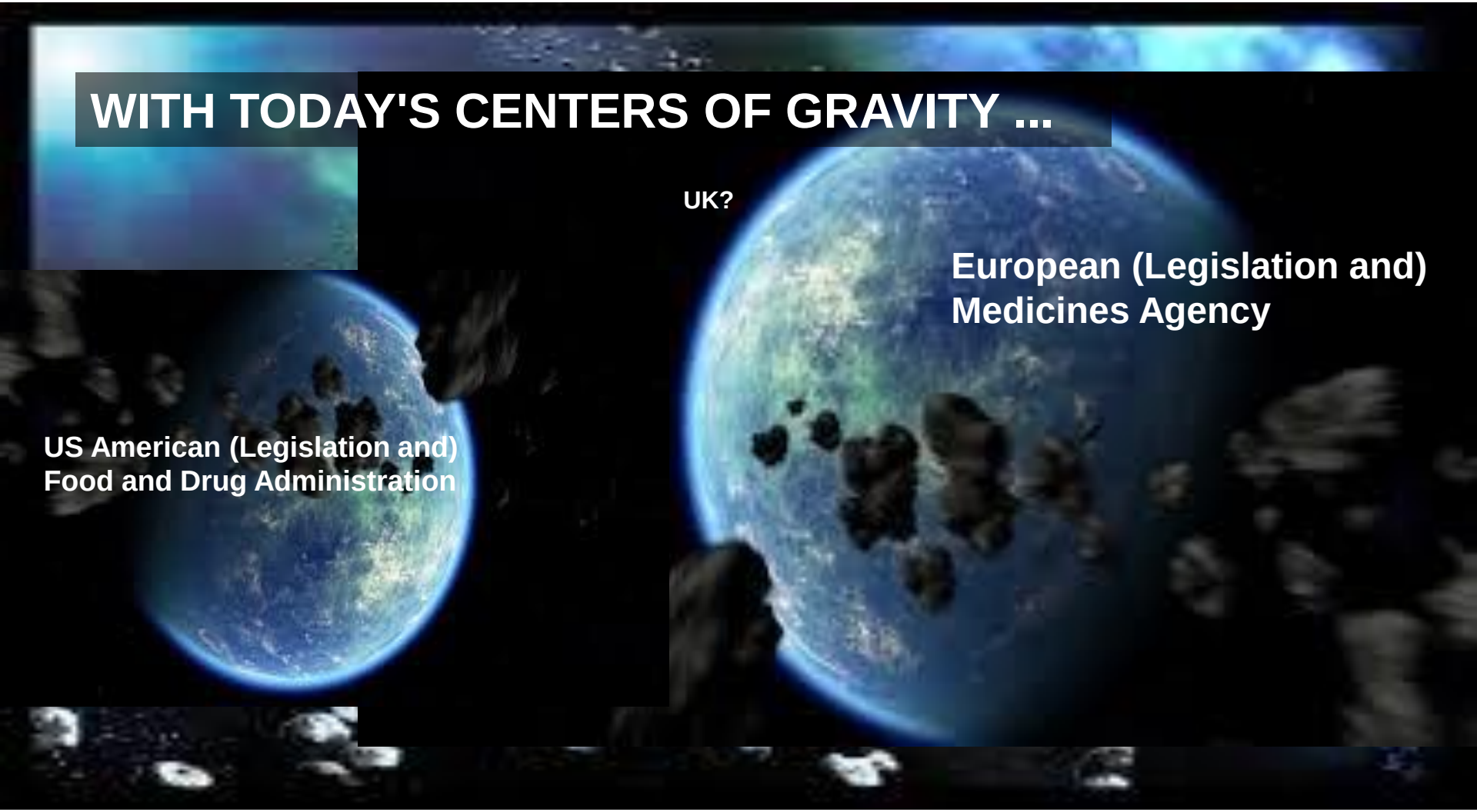
- Pro-active QC

Still relevant with Plasma – as with any Bio Product

- Immunology – therapeutic target but also source of unpredictable ADR
- Manufacturing changes – to be assessed as potential source of ADR
- Off label use – to be considered in safety like established use

one last time – back to EU PV
in the Global context .....

a "System" Heavyweight



.... currently dominating a companies global PV system

Biotest
From Nature for Life

country B
most strict special
unspecific basis
country
most strict special
unspecific basis
country A
most strict special
unspecific basis
country E
most strict special
unspecific basis

unspecific basis

Currently the EU PV requirements appear most strict in almost every aspect – with impact on a Global PV System

.... the world copies ... PSMF and QPPV

Biotest
From Nature for Life

Russia

Saudi Arabia

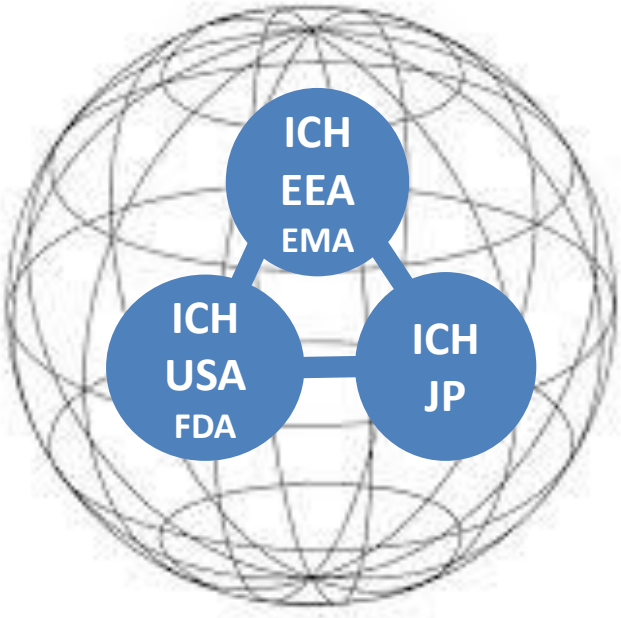
UAE

who's next?

a final utopia? on PV Methodology ...

WHO → **"WMA"?**

Pharmacovigilance is needed in every country,
because there are differences between countries (and even regions within countries) in the occurrence of adverse drug reactions and other drug-related problems. This may be because of differences in: drug production, distribution and use (e.g. indications, dose, availability) genetics, diet, traditions of the people ..



but not necessarily with different methodology in monitoring and evaluation.

http://apps.who.int/medicinedocs/en/d/Jh2934e/2.html#Jh2934e.2