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Patient Risk Management Plans

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AstraZeneca

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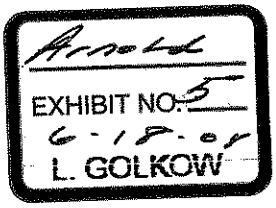

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Why is risk management necessary?

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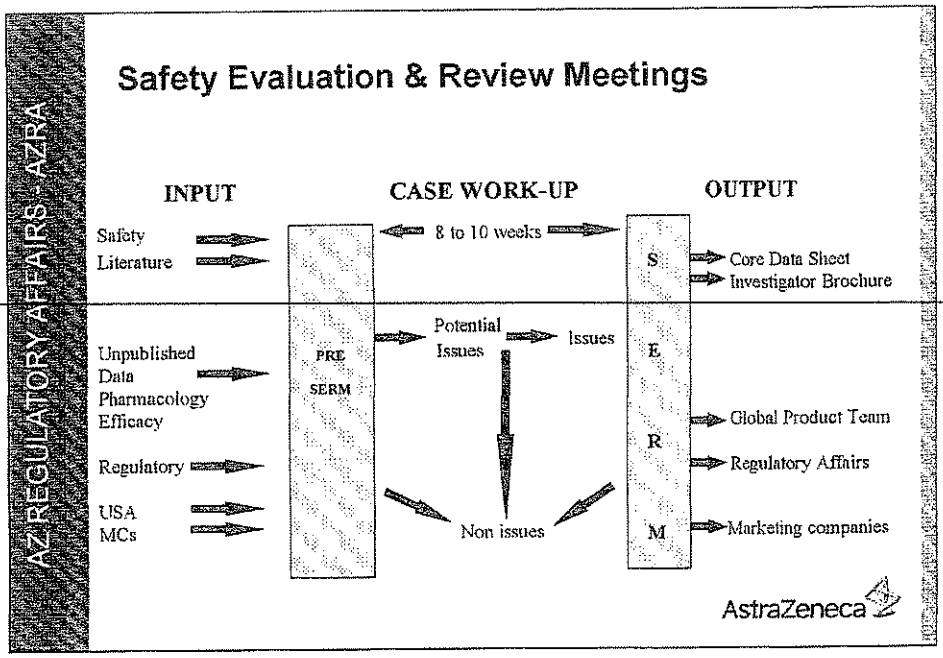
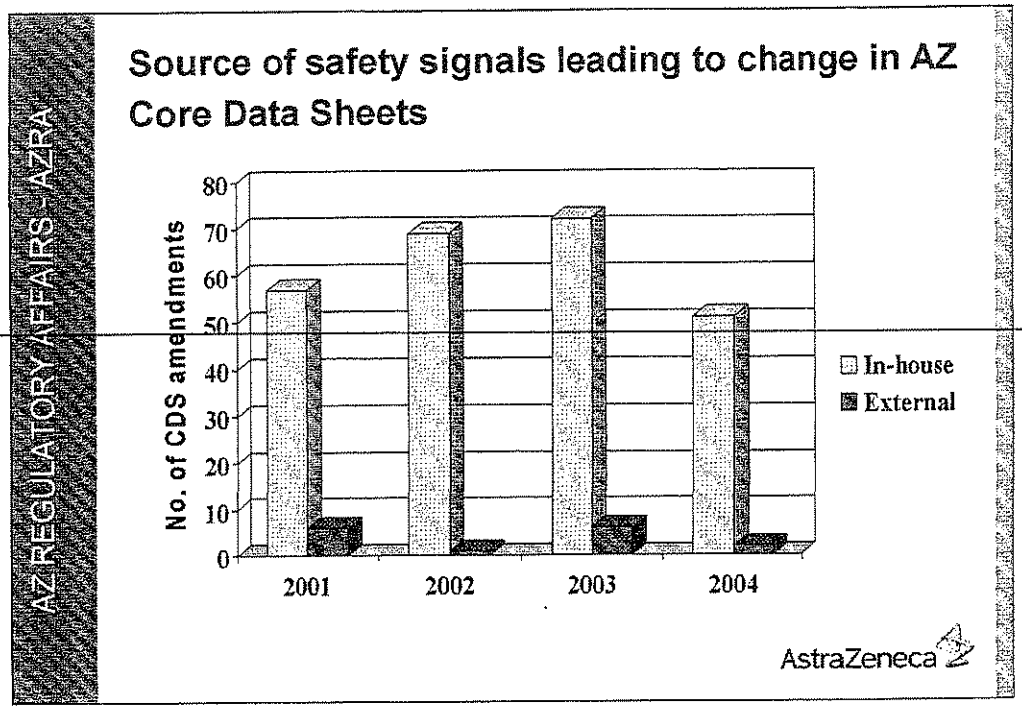
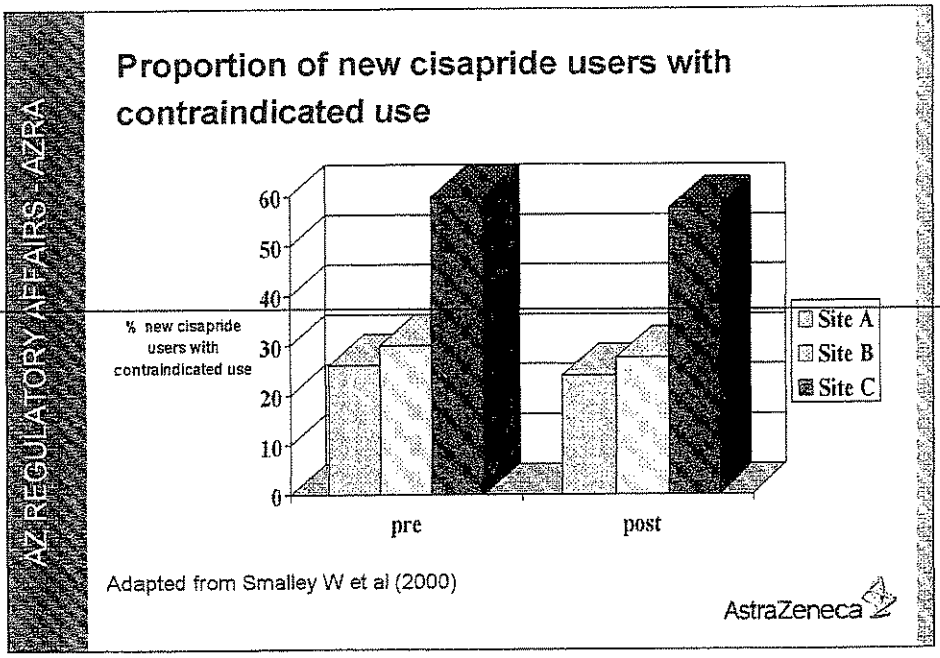


Risk management is evolution of existing processes.



This slide demonstrates how effective SERM is as a signal generation and evaluation process: the great majority of resultant changes to our core prescribing texts, and ultimately the local labels, arise from signals generated within AstraZeneca rather than from external sources e.g. FDA or other regulatory authorities, publications etc.



Probably the key publication to throw doubt upon the effectiveness of prescribing texts as a risk management tool. Substantiated by other publications and subsequent experience.

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Cisapride - package insert

The 2-page package insert for cisapride when printed in 12-point font on 8.5x11 paper is more than 10 pages long and contains more than 470 facts about the drug.

Woosley RL (2000). JAMA 284 (23) pp3047-3049

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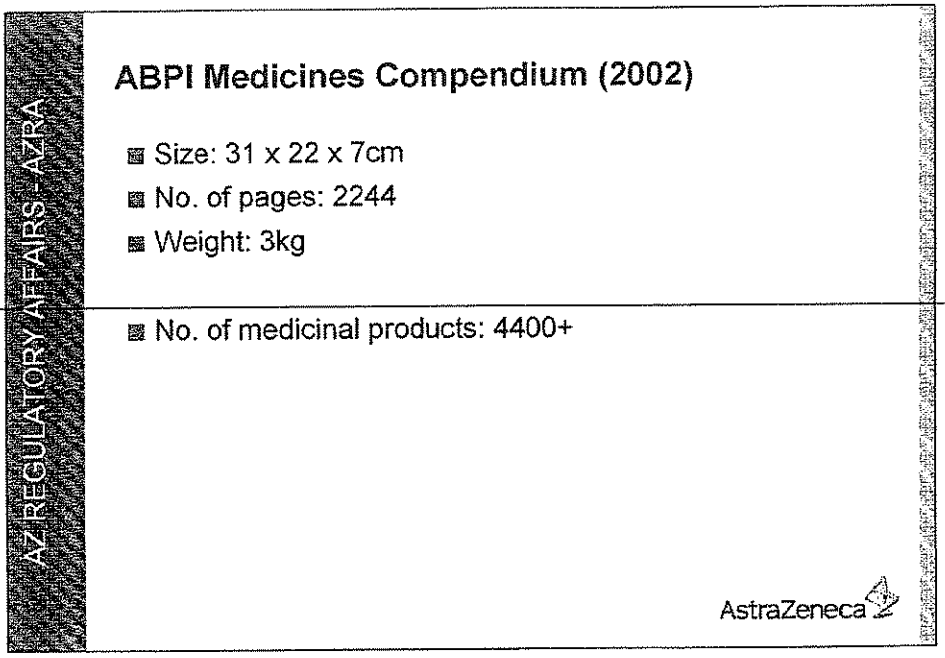
No wonder physicians do not read the label!

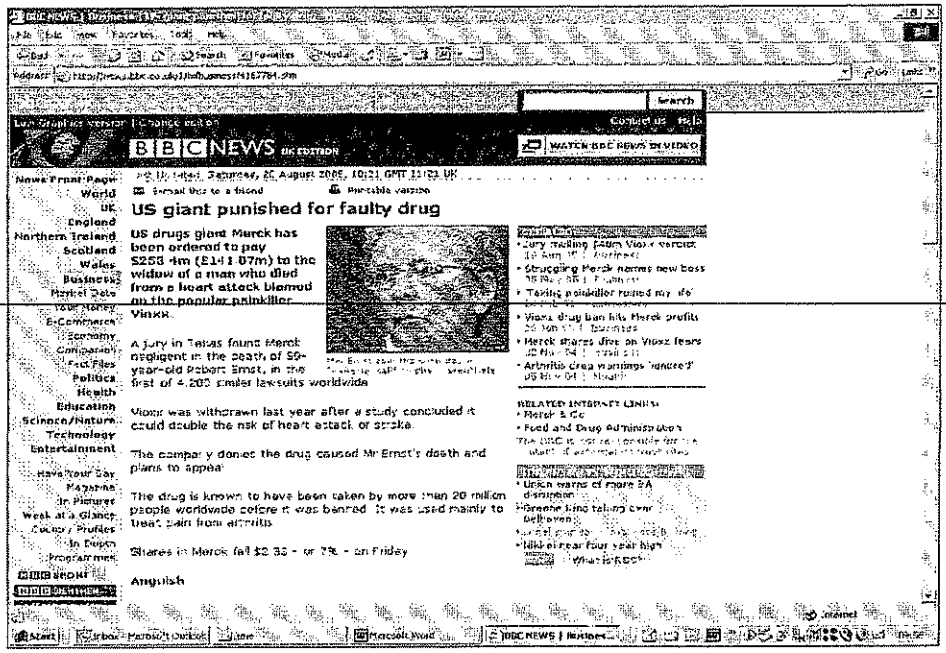


The issue is not restricted to the USA.


US government agency to investigate FDA over rofecoxib

Pfizer criticised over delay in admitting drug's problems

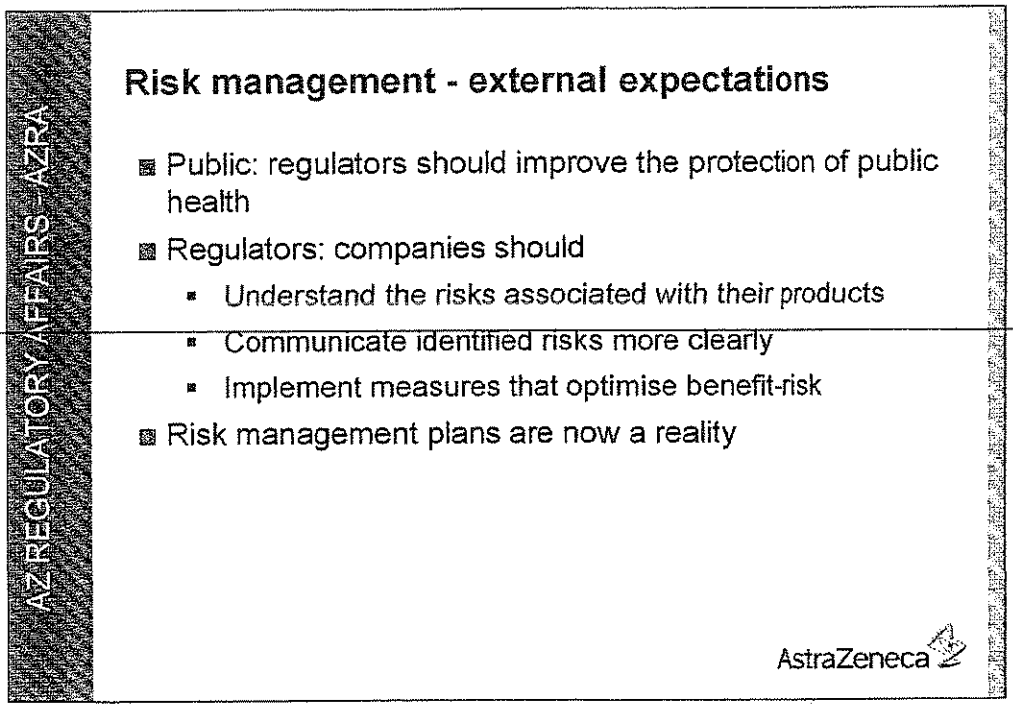
Vioxx has raised the stakes dramatically. The safety of medicines, and the industry's response is now very much in the public eye.



Situation further exacerbated by the Texas verdict in Aug 05. Companies that do not act appropriately in managing the risk of products could face huge punitive penalties, in tens of $billions. Merck may face up to $10billion in costs due to Vioxx.

Note: Wyeth have already paid out $12billion in compensation for Fen-Phen.

It is becoming a nightmare for the industry, and for Drug Safety departments.



The public expects the regulators to act – the latter are now becoming very risk averse. Regulators expect industry to raise its standards.

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EU Regulatory Requirements

- **Regional requirements:** EMEA require "The submission....of risk management plans in the context of marketing authorisation applications" from November 2005
- **National requirements:** Likely to vary; may require local risk mitigation plans that specifically outline local MC activities
- **European Risk Management Strategy Working Group** (ERMS) established by EMEA; activities ongoing:
  - May 2005 'Action Plan' indicated that CHMP PhVWP will be the advisory body for PRMP-related activities.
  - 'Rapporteur' type approach to assessment is suggested
  - Specific requirements for content of PRMPs published in draft CHMP guideline implementing ICH-E2E

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Patient Risk Management Plans

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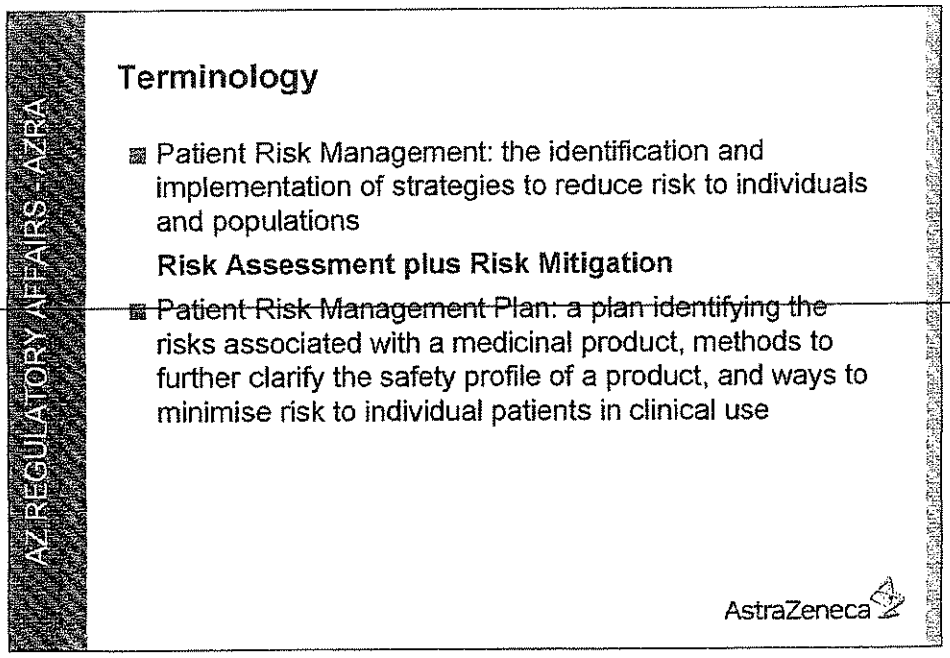

Risk management includes measures to reduce risk. May need to be very active.

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Patient Risk Management Plans

- Each plan should be unique for the product under consideration
- Should address all aspects of risk management; include concepts presented in the ICH E2E guideline
  - ~~Safety Specification~~
  - Pharmacovigilance Plans

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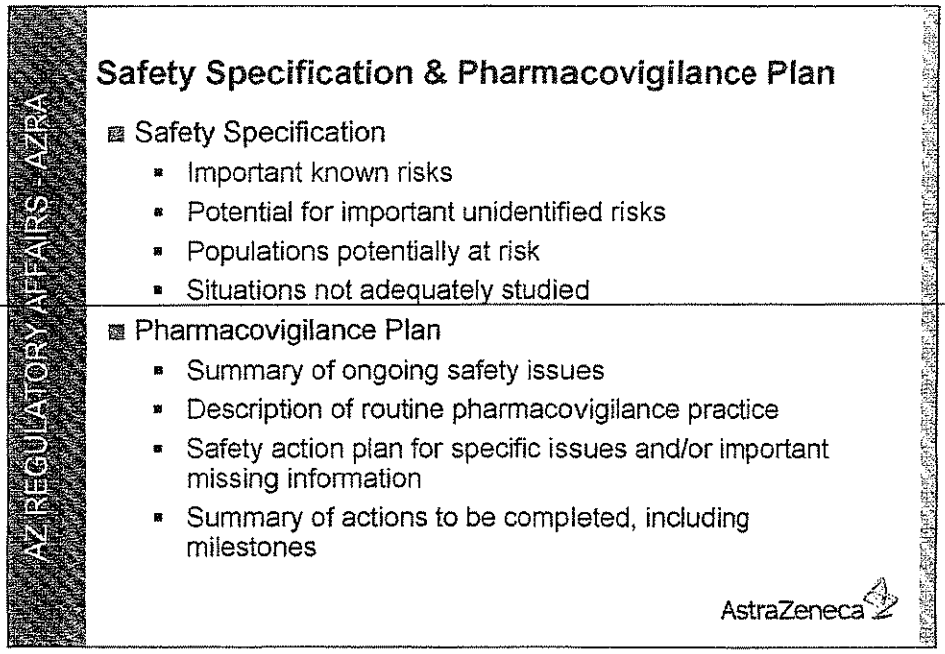
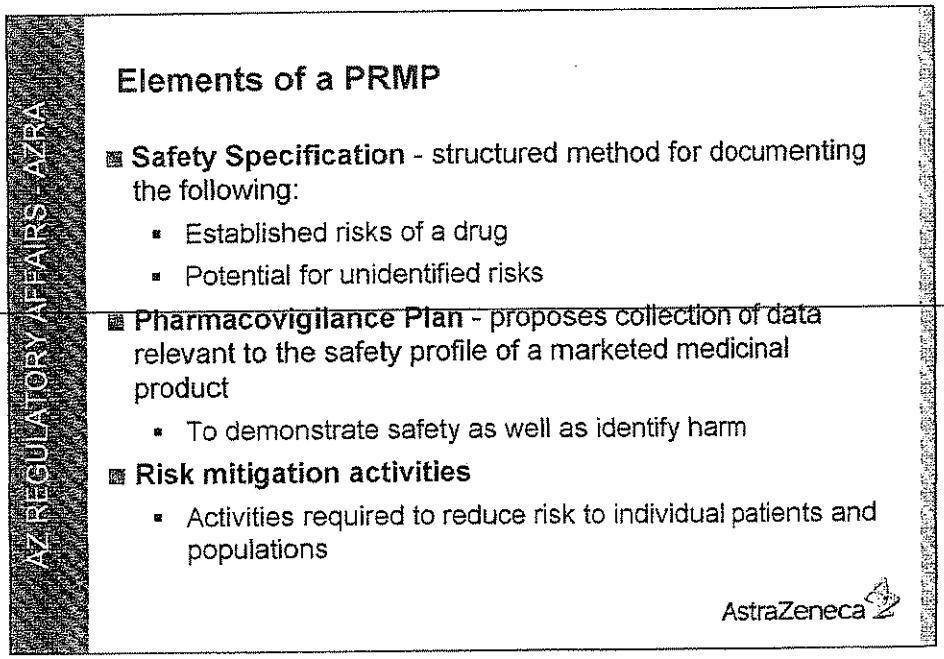


EU regulators expect all PRMPs to include a SS and PP in accordance with ICH E2E.

Note that ICH requires a focus on 'important' risks. Not all risks will necessarily require further assessment or mitigation. A risk that is considered fully characterised, labelled and not requiring specific mitigation activities might not actually be included within the Safety Spec. The point is that there subjective medical judgement is required in determining the important risks that require specific assessment or mitigation measures.

Historically some pharmaceutical companies might have been reluctant to proactively document potential risks and how they're assessing them. AZ will be taking a more proactive approach and therefore we need to make sure that the documents are worded appropriately a clearly differentiate what we do or do not consider to be a causally-related risk compared with a potential risk. Legal review of PRMPs is also part of the process.

Populations potentially at risk may not include the intended population (is there a foreseeable risk of off label use for example).



ICH E2e does not cover risk mitigation. But PRMPs require this in addition to SS and PP.

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Risk mitigation activities

- All products: high quality pharmacovigilance & product labelling
- Some products: may require specific intervention to mitigate risk, e.g.:
  - Information directed at prescribers, pharmacists and/or patients
    - Patient educational programs
    - Healthcare provider education programs
    - Certification programs for prescribers and pharmacists
    - Additional education forums
  - Specialised packaging
  - Controlled access and/or product distribution channels

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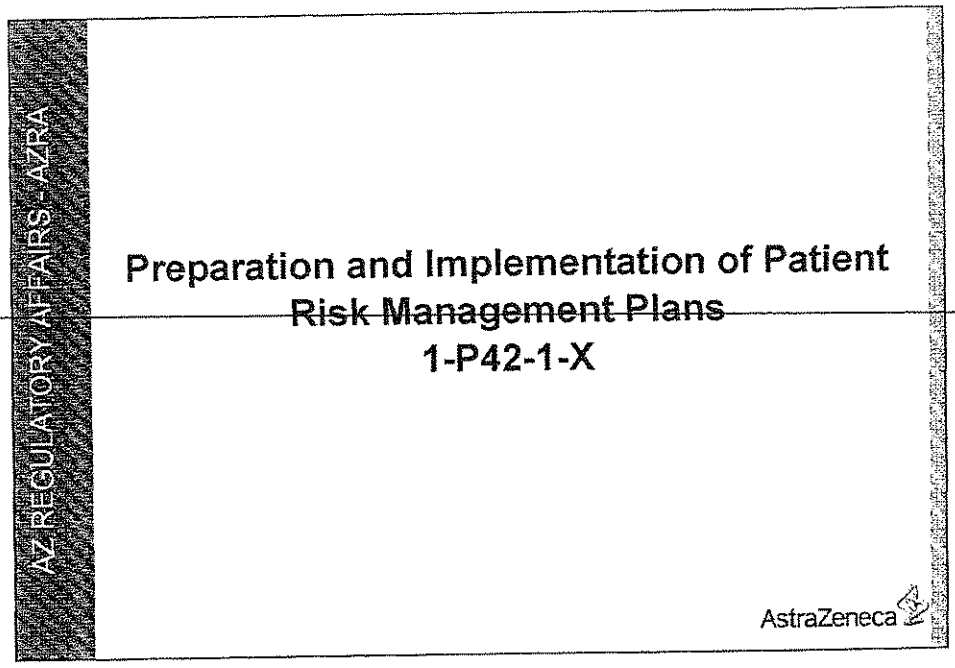
EU regulators have made it clear that they expect most new products to include measures over and above product labelling and pharmacovigilance.



New cross-functional SOP – already effective, but subject to training and education of all parts of business during 4Q05/1Q06.

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International Procedure 1-P42-1-X

- Provides a framework to produce and implement the plans themselves
- Covers much of the product lifecycle and stresses the requirement for cross-functional input
- Detailed procedure needed to encompass the range of activities and responsibilities
- But.....
  - The new procedure and the resultant PRMPs won't truly deliver effective patient risk management, unless accompanied by the right business behaviours
  - Behaviours across AZ need to embrace the demands of the external environment and encourage a proactive risk management culture

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PRMP Procedure (1)

- PRMPs to be key element of AZ commitment to ensure that its products are used in a manner that delivers optimal benefit-risk
- SOP describes mandatory requirements for preparation, approval, implementation, archiving and revision of PRMPs
  - Includes individual accountabilities and responsibilities
  - EPT/GPT remit to include development and implementation of PRMPs

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PRMP Procedure (2)

- PRMPs to be initiated prior to first human exposure; focus will evolve during product lifecycle
  - Early development: safety of participants in clinical trials
  - Post-TG3: preparation for registration and post-marketing activity
    - Increasing need for input from other functions and marketing companies

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PRMP Procedure (3)

- Single 'global' PRMP for each product
  - To include safety Specification and Pharmacovigilance plan, plus broad risk mitigation strategies
  - European RMP to be prepared for EU submission
  - Global/European RMP provides template for Local RMPs
    - Meet local regulatory requirements
    - Meet local variations in healthcare practice
    - Must include mandatory elements of global PRMP

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PRMP Procedure (4)

- SOP now effective
- Extensive training and education package in preparation
  - Modular approach
  - Clinical Drug Safety to take lead role in delivery

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Regulatory Affairs Directors Responsibilities

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RAD Responsibilities

- Ensure that the PRMP addresses global regulatory requirements and standards for patient risk management
- Review all versions of the PRMP as part of the EPT/GPT
- Collate any information provided by local AZ Regulatory Affairs personnel on regulatory authority requests to amend LRMPs, and communicate this to the GPD, MSD and GDSP

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Local AZRA responsibilities

- Review and approve all versions of LRMPs for their market, to confirm that the LRMP meets local regulatory requirements
- Ensure appropriate local AZRA participation in LRMP delivery teams
- Ensure that the document format of the LRMP is appropriate to meet national regulatory requirements
- Ensure that risk mitigation activities proposed in LRMPs are appropriate to address national regulatory authority concerns relating to patient safety
- Ensure the GRAD is informed about any national regulatory authority feedback relating to the LRMP for their market

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Patient Risk Management Plans

Schematic Overview of Process

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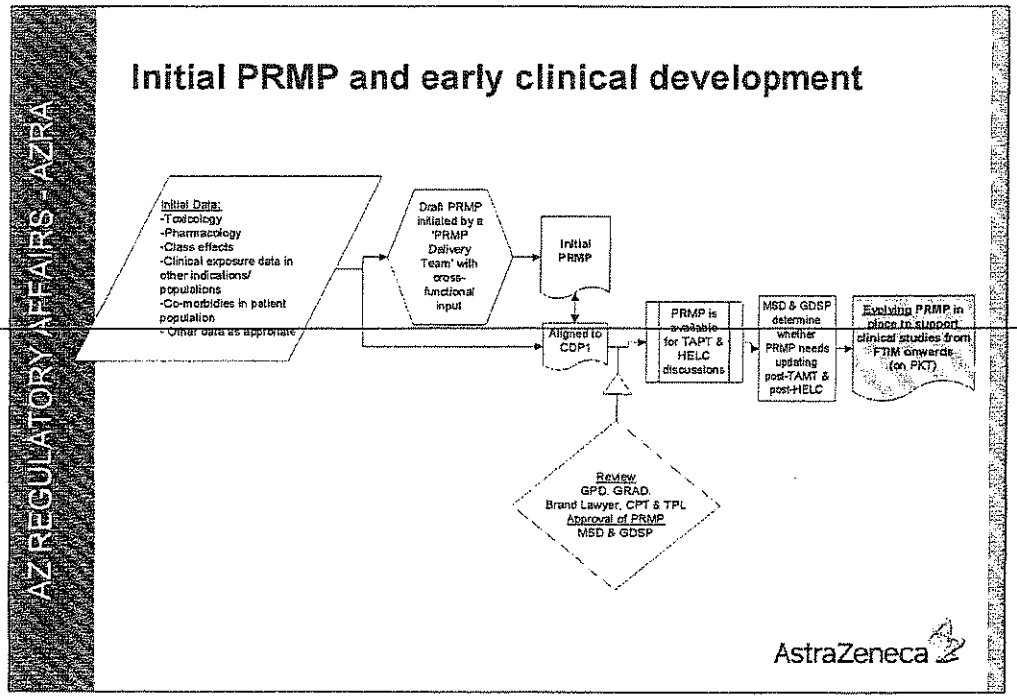


PRMP = Patient Risk Management Plan

CDP1 = Clinical Development Plan 1 (the first version of the CDP, developed by the Clinical Project Team

GDSP = Global Drug Safety Physician

MSD = Medical Science Director

GPD = Global Product Director

GRAD = Global Regulatory Affairs Director

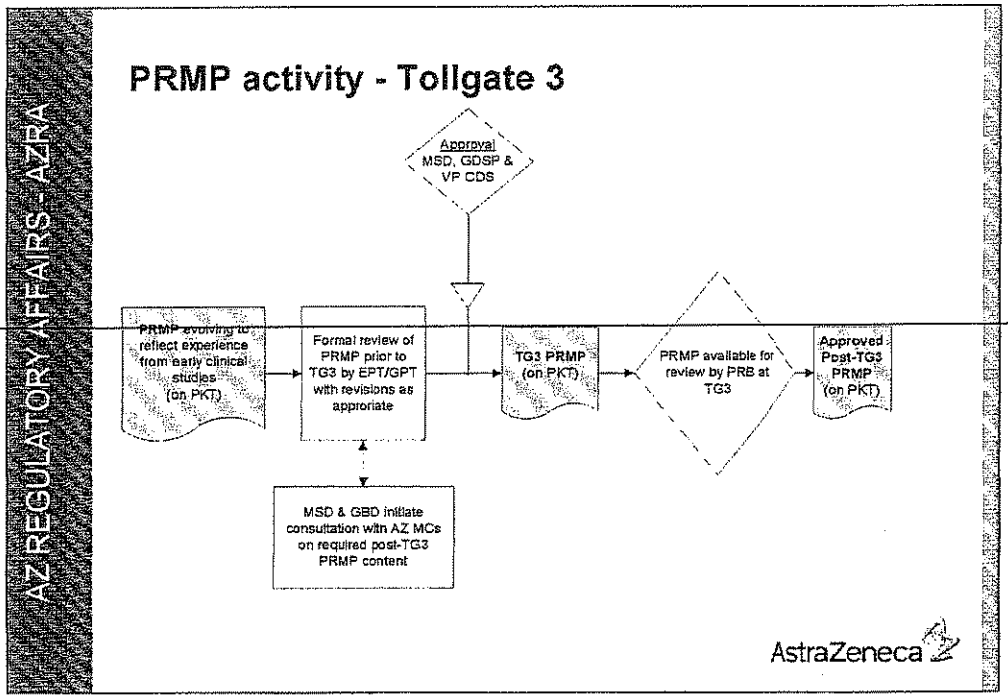
CPT = Clinical Project Team

TPL = Toxicology Project Leader

TAPT = Therapy Area Project Team

HELC = Human Exposure Limits Committee

PKT = Product Knowledge Transfer (an internal AZ document storage system where strategic Global Product team documents are stored electronically)



PRMP = Patient Risk Management Plan

GDSP = Global Drug Safety Physician

MSD = Medical Science Director

GPT = Global Product Team

EPT = Emerging Product Team

GBD = Global Brand Director

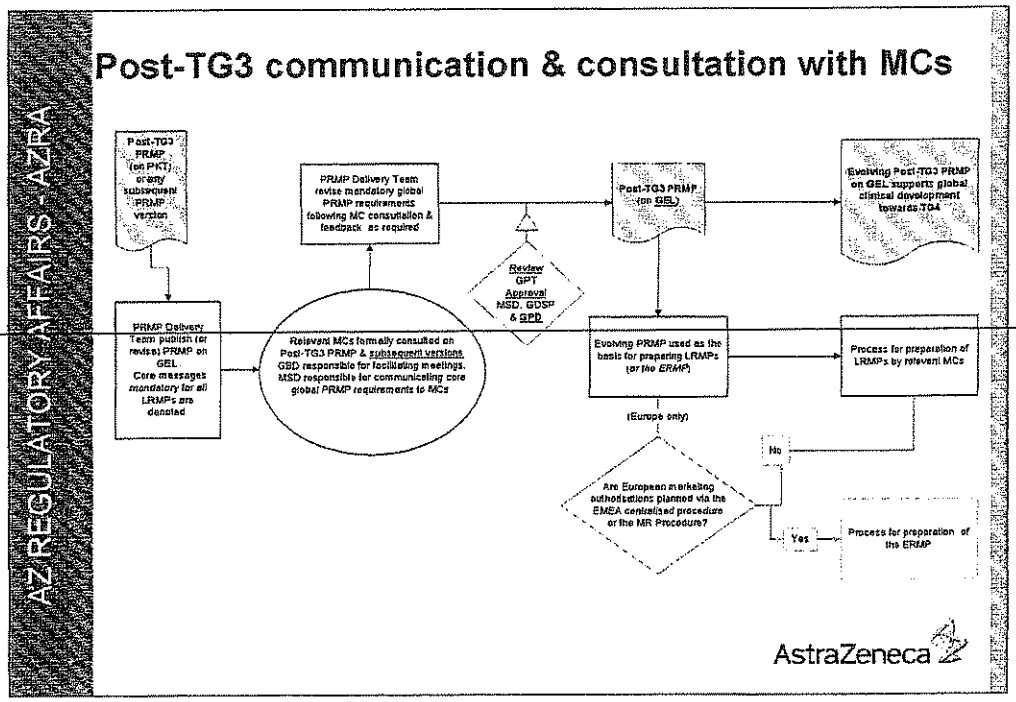
AZ MCs = AstraZeneca Marketing Companies

TG3 = Tollgate 3 Decision Point

VP CDS = Vice President, Clinical Drug Safety

CPT = Clinical Project Team

PRB = Product Review Board



TG3 = Tollgate 3 decision point

PKT = Product Knowledge Transfer Database (housing internal AZ documents)

GEL = Global Electronic Library database (housing documents used for regulatory submission purposes)

PRMP = Patient Risk Management Plan (Global document)

LRMP = Local Patient Risk Mitigation Plan (Country-specific local document)

ERMP = European Risk Management Plan (Regional European level document)

MC = Marketing Company

GBD = Global Brand Director

MSD = Medical Science Director

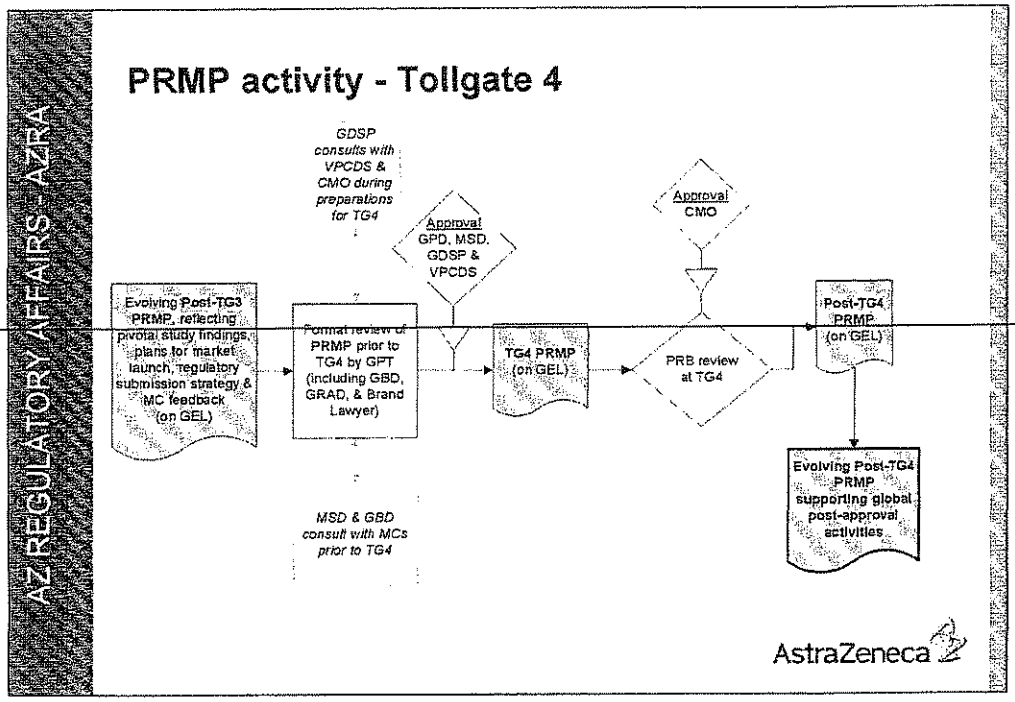
GPT = Global Product Team

GDSP = Global Drug Safety Physician

GPD = Global Product Director

MR = Mutual recognition (a European regulatory approval process)

TG4 = Tollgate 4 decision point



TG3 = Tollgate 3 decision point

VP CDS = Vice President, Clinical Drug Safety

CMO = Chief Medical Officer for AstraZeneca

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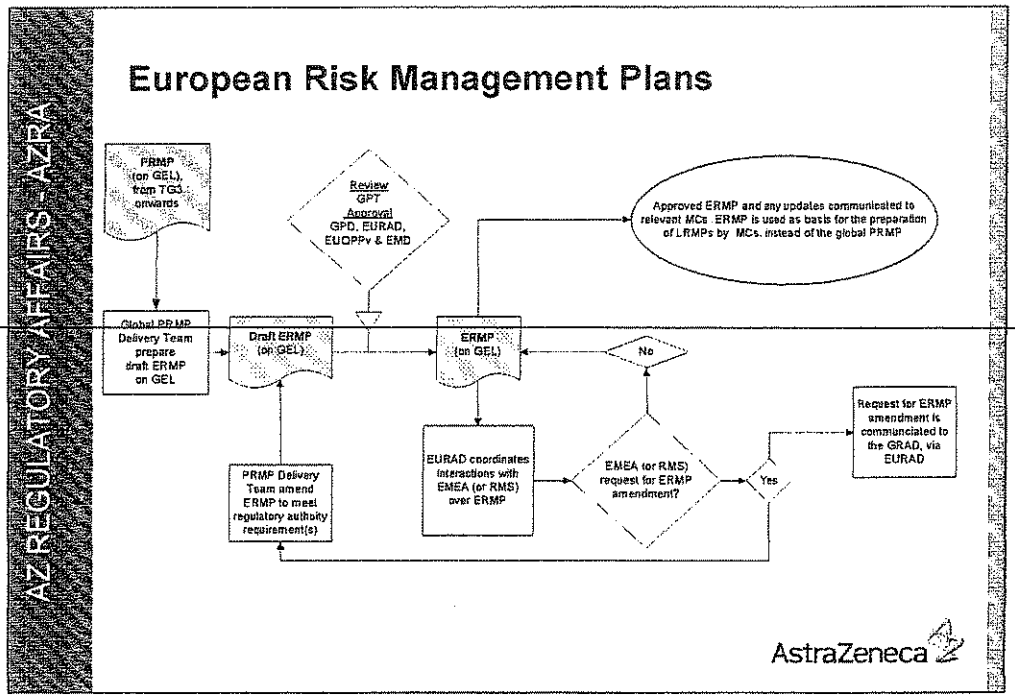

TG3 = Tollgate 3 decision point

ERMP = European Risk Management Plan

EURAD = European regulatory Affairs Director

EUQPPv = European Qualified Person in Pharmacovigilance

EMD = European Medical Director

RMS = Reference member State

EMEA = European Medicines Agency

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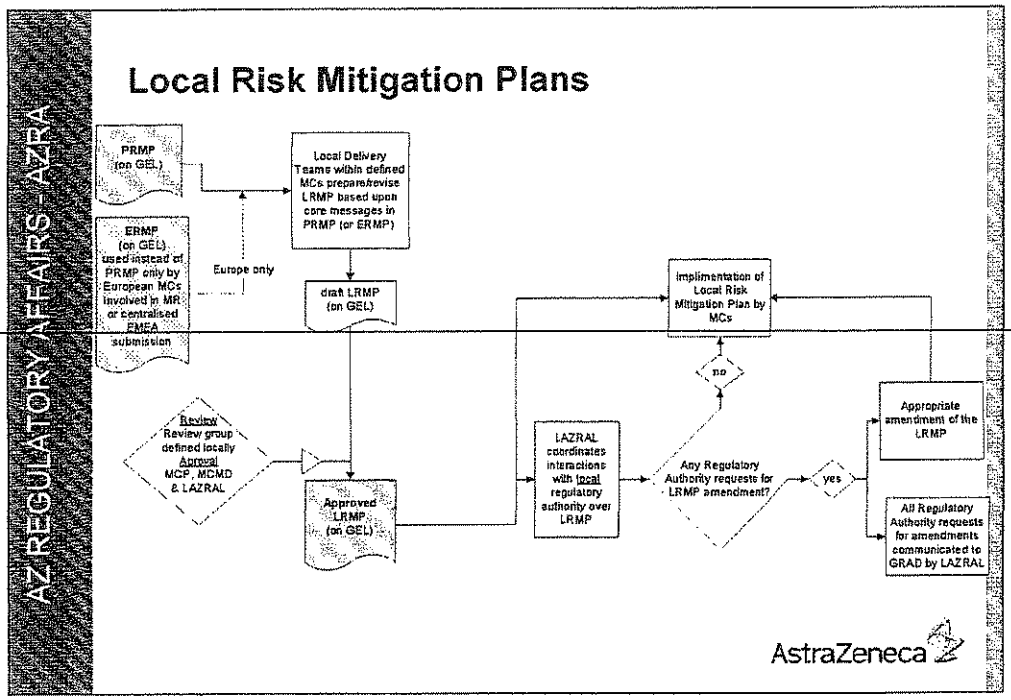

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EMEA = European Medicines Agency

MR = Mutual Recognition Procedure

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ERMP = European Risk Management Plan (Regional European level document)

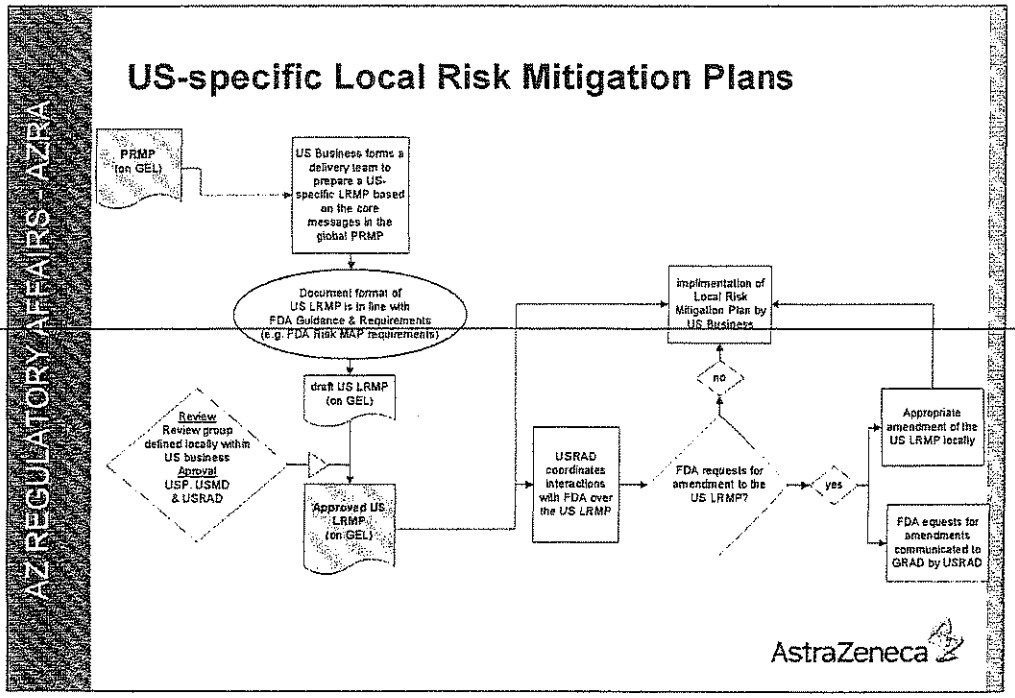
MC = Marketing Company

MCP = Marketing Company President

MCMD = Marketing Company Medical Director

LAZRAL = Local AstraZeneca Regulatory Affairs Leader

GRAD = Global regulatory Affairs Director



PRMP = patient Risk management Plan (Global document)

GEL = Global Electronic Library

US = United States

LRMP = Local Risk Mitigation Plan

FDA Risk MAP = The FDA's guidance on Risk Mitigation Action Plan (MAP) Requirements

FDA = Food & Drug Administration (US Government)

US LRMP = US-specific Local Risk Management Plan (a.k.a AstraZeneca's FDA Risk MAP for the product)

USP = President of the US AstraZeneca Business

USMD = US Medical Director for AstraZeneca

USRAD = US regulatory Affairs Director for the product

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