Workshop objectives

1. To review current regulatory practices in the region.
2. To identify possibilities for harmonisation of regulatory systems in the region.
3. To identify Best Practices within and outside the region.
4. To exchange ideas on how improvements could be made to existing practices.
5. To identify the value of a regional network of agencies.
Session Topics

1. Dossier Structure
2. The Scientific Review Process
3. Use of Experts
4. Opportunities and Benefits for Harmonisation and Mutual Recognition

Abbreviations used in this presentation:
APVMA:
Q & A: questions and answers
MRP: Mutual Recognition Procedure
EAC” East African Community
RC: Reference Country
CC: Concerned Country
CGMR: Coordination Group for Mutual Recognition
MR-C: Mutual Recognition Co-ordinator
AR: Assessment report
ATU: L’autorisation temporaire d’utilisation / Temporary Authorisation
SOP: Standard Operating Procedure
SPC: Summary of Product Characteristics
VICH: International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.OIE: Organisation for Animal Health
OIE: World Organisation for Animal Health
EAEU = Eurasian Economic Union
ASEAN = Association of Southeast Asian Nations
SADC = Southern Africa Development Community
ZAZIBONA = Zambia, Zimbabwe, Botswana, Namibia
Dossier Structures

- Typical structure
  - Part 1: administrative info and summary of product characteristics, labelling and package leaflet
  - Part 2: manufacturing method, quality control, stability
  - Part 3: pharmacology, pharmacokinetics, toxicology and safety (user and environment), metabolism and residues.
  - Part 4: clinical data: tolerance and efficacy in target species

- Templates and guidelines on content

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1. Dossier Structures

Regulatory Terminology:
- Medicine = drug, or pharmaceutical & biological?
- Marketing Authorisation (MA) or Product Licence
- Registration – issuing a registration number?
- Regulatory Authority – assesses registration dossiers; issues Marketing Authorisations
- Issuing Import Permits versus Medicines Registration

1.1 Are there different dossier formats for:
- Human Medicines
- Veterinary Medicines
- Veterinary Biologicals
Establishing Registration Systems

Normal sequence for development of Regulatory Requirements

1. Human Medicines Regulations

2. Veterinary Pharmaceuticals

3. Veterinary Biologicals
Biologicals are not Pharmaceuticals!

Question - What is the easiest option for introducing a registration system for biologicals?
Answer - copy/paste legislation and guidelines directly from pharmaceutical documents.

But this is not appropriate because:
compare the modes of action
- Pharmaceuticals – pharmacological
- Vaccines - immunological
What is the difference?

Pharmaceuticals

Not necessarily pharmaceuticals

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Use of the same application form for vaccines and pharmaceuticals is not advisable unless the application form does not include any technical information.

- The composition is expressed in different terms.
- The criteria for batch release are quite different.
- The dosage for vaccines is not expressed in mg/kg bodyweight.

The use of WHO guidelines as standards for veterinary medicines, especially vaccines, is often inappropriate. Example: WHO expects injectable medicines to be terminally sterilised, however this will of course destroy the antigen/microorganism in a vaccine.

The OIE guidelines are appropriate for veterinary vaccines and should be used by assessors. VICH guidelines appropriate for vaccines include GL44 on Target Animal Safety testing.
1.1 Questions about Dossier Structure

1. What dossier structure do you currently use?
2. Is it appropriate for the type of medicine?
3. Is the structure published?
4. Are there any similarities within the region?

Notes

Do you provide guidelines or templates for the information to be included on the packaging and package leaflet?

These details should reflect the claims and warnings that regulatory assessors approve in the Summary of Product Characteristics. These details should all be supported by evidence provided in the registration dossier.
3.1 Timelines and Organisation –

As an agency, we have a choice to allow dossiers to be submitted only when completed (e.g. EU EMA), or to allow phased submissions (e.g. US FDA).

The most typical method is the acceptance of complete dossiers only. The biggest advantage of such approach is obviously that it is easier to manage and plan your reviewer-resources at the agency, while you also have a better view on the “technical validity” of the entire dossier. Does it indeed contain all the data elements expected? Is something missing? There is also less unpredictability from partial submissions.

The model of this type of review is in the EU procedures, where also very strict timetables are being published for submission dates, aligning procedures with meeting dates of the review committee.
Phased submissions allow the applicant more flexibility as not all sections have to be finished before the first sections can already be assessed. This should theoretically result in a shorter review time, and may allow any issues in these parts of the dossier to be identified earlier. After a first administrative opening of the dossier review, at least a manufacturing part, safety part and efficacy part have to be submitted. Typically this is followed by a final admin section with for instance final label and printed packaging material. The biggest issue here will be the lack of predictability of the different partial submissions and also uncertainty if a dossier will be completed.

The model of such review is with the US FDA where you open the procedure with a so called INADA (Investigational New Animal Drug Application) and you end after the partial submissions with so called “NADA” or New Animal Drug Application to close the procedure.

Predictability of timelines once a review has started is a key issue for all stakeholders.
Actual review

Obviously, the general objective of the assessment of the dossier submitted is to check whether there is sufficient benefit of the use of the product, while there is no unacceptable risk associated with such use.

The four main sections of a typical dossier reflect the 4 questions you will have

1. What are the details of the product in terms of label, information, packaging material, manufacturers etc
2. Is the quality good enough,
3. Is the product safe enough?
4. Does it work and deliver benefits?

The overall objective is to come to a reasoned conclusion about whether the benefit-risk balance of the product is positive or not
On the product quality we consider whether we can expect a high quality product
Consistently manufactured (using appropriate standards, such as GMP)
Are the starting materials, the intermediates and the manufacturing process sufficiently specified?
Will the stability be sufficient to guarantee product efficacy but also safety throughout the shelflife? Were the conditions of that study adequate?
Were there only accelerated stability studies for a shorter time period?

Do we have enough information on what specifications would be sufficient to describe the essential characteristics of the product?

The key here is to understand what the appropriate quality should be. Asking for oral fish vaccines to be produced using a sterile carrier is goldplating as the vaccine will be thrown into water containing feed and also excreta!
This is particularly critical when assessors are for instance all pharmacists, working predominantly for human medicinal products
The safe use of any VMP is of course paramount and pivotal for the assessment. Unlike in human medicine, a consumer safety is an important issue as we do for instance eat many of our patients...

So the different aspects do not only cover acute and chronic exposure of target animals and the effect of that on reproduction as well, we also cover human safety from different angles. Not only the safety of owner or farmer or veterinarian administering the product needs to be guarded, but also for food animals the safety of food of animal origin from treated animals.

So typical veterinary concepts of MRL and residue depletion as well as withdrawal period are examined in this section.

The proof of efficacy is of course a corner stone and probably the most important section. This is where the benefit of the use of the product needs to be proven.

Overall, a lot of questions need to be answered. As agencies also have resourcing issues and in order to improve availability of products on the market, (re)using assessments done by other countries or regions can be a big time and resource saving instrument while still safeguarding the standards of quality, safety and efficacy.
Often we think about a licence as something you approve. Sometimes applicant’s requests are rejected. In case an applicant believes this is not a correct decision, an appeal should be possible. Appealing could happen against a complete rejection or to a part of a decision.

- Appeal need to **run like a normal procedure**
  - Clear rules for eligibility
  - Clear rules for procedures
    - Organization and timelines
      - New data may be requested by reviewers
      - Short time allowed
  - Who will do the second scientific review?
    - The same people?
Questions about The Scientific Review Process:

Timelines, Organisation & actual Review

► Does your system need complete dossiers or are phased submissions acceptable?
► Do you have your assessment organized “all in-house” or do you use external experts?
► Do you have fixed timelines in your legislation for the review?
  • If so: what are the biggest benefits and issues you encounter?
  • If not: what are the drivers not to set defined timelines?
► Is there any option for an appeal by the applicant?
  • If so: will it be reviewed by separate resources?

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The interaction with applicant can be

- Minimal:
  - at submission and/or asking questions and communicating outcome

- More commonly
  - Before submission (purpose = increased quality of submission)
  - During submission (purpose = making sure your questions are understood (and can be answered))
  - After submission (purpose = good communication and compliant marketing)

Could create real win-win situation
When interacting with the Applicant

Transparency is key: exchange with scientific reviewers and the applicant are to be well-framed

- Leads to more predictability (not less requirements!) and improved quality of submissions
- Leads to more trust in the system
- But, exchange with scientific reviewers and the applicant needs to be well-framed
Fast-track procedures

Why do you / would you need it?
- Exceptional and severe circumstances
- Example: emergency vaccines, e.g. blue tongue

Main outcomes are Temporary or Conditional Licences
- Temporary Licence to Use (authorisation temporaire d’utilisation or ATU) in France to deal with “sanitary situations”
- Provisional licence – UK
- Temporary license for “compassionate use” in many countries both human and vet
- Conditional licences in many countries
  - Mostly to allow providing of confirmatory but not critical data later
  - Most common: accelerated stability data to be followed up with full data package

Questions

Do you need these fast-track and conditional procedures?
Are these allowed in your country? How are they used?
Would you like to change that situation?
Why do you need such guidelines, standards and tools?

- Consistency of decisions in time and between assessors
- Transparency towards the public and applicants on
  - On what basis decision is made
  - how decision is made
- Partially internal guidelines, tools and “job aids”, partially “public” procedures and requirements

Internal guidelines and tools for consistency and transparency

Why do you need such guidelines, standards and tools?
- Consistency of decisions in time and between assessors
- Transparency towards the public and applicants on
  - On what basis decision is made
  - how decision is made
- Partially internal guidelines, tools and “job aids”, partially “public” procedures and requirements
Several layers of such standards are available

INTERNATIONAL/GLOBAL
  - VICH and OIE Guidelines;
REGIONAL
  - European Pharmacopoeia
  - Regional legislation if available (e.g. EU)
and NATIONAL,
  - US Code of Federal Regulation, national laws and decrees
  - SOPs – e.g. how to write an assessment report
  - Templates – SPC, container label / assessment reports
  - Guidelines – for assessors / for applicants / for GMP inspectors

Questions:

Do you have sufficient guidelines and tools available in your country to provide transparency and consistency?
Would you use/borrow/“translate” guidelines from another region or country?
Questions about The Scientific Review Process

2.1 Interactions with the Applicant
- Are your evaluators/assessors approachable?
- Have you build into your system moments for interaction
- How do you prevent “undue” influencing, while allowing interaction?

2.2 Fast Track Procedures
- Do you need these fast-track and conditional procedures?
- Are these allowed in your country? How are they used?
- Would you like to change that situation?

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2. Questions about the Scientific Review Process

2.3. Internal guidelines and tools

Fast-track procedures
Why do you / would you need it?
Exceptional and severe circumstances
Example: emergency vaccines, e.g. blue tongue

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Questions
Do you need these fast-track and conditional procedures?
Are these allowed in your country? How are they used?
Would you like to change that situation?
The need for experts?

- The assessment and review of dossiers for (veterinary) medicines is a complex and specialised project.
- An agency needs to be able to provide both resources for the administrative and scientific management of the applications.
- But
  - Resources are often “not abundant”
  - Safety and efficacy, but also the chemistry-pharmacy part of the dossier requires a high level of expertise
  - Technology changes and expertise needs to be kept up to date
  - Often “company scientists” know “more” (because they developed the product)
- Different solutions or possible
  - For instance in the US: scientific departments with many government scientists ensure all assessments can happen in house
  - Some agencies have no “internal” scientists
- So how can experts help you assessing a dossier?
3. What is the role of experts?

- Facilitate the assessment of the dossier
  - Faster, as they summarise the information
  - Easier, as they provide specialised knowledge
- Expert needs to be critical...
- An expert can only provide an opinion, not a decision

The role of Experts:
- In general experts should be able to facilitate the dossier assessment, because
- They allow more dossiers to be processed in the time available by providing more resources
- They allow assessment of technologies that are not known to your staff, or they allow assessment of aspects you don’t have expertise in
  - E.g. pharmacists can easily handle manufacturing data, veterinarians may have an easier time assessing efficacy, but having regulators that know everything is difficult
- Experts need to be critical. In the dossier there often is already a summary of the data written by the applicant. A summary of a summary will not really help or facilitate your assessment.
- Experts can help you understand and can explain things to you. The regulatory agency remains accountable for the assessment and the ultimate opinion or decision!
3. Types of expert

**Experts appointed by Applicant**
- To write Expert Reports on parts of the dossier
- For “manufacturing” part often a company expert
- For safety and efficacy often external, academic or consultant experts

**Experts appointed by Regulatory Authorities**
- To help with dossier assessment
- Typically when resources are stretched
- Can be part of “scientific board”

**Experts appointed by Applicant from list of experts provided by Authorities**
- E.g. Australia’s APVMA: working with “accredited experts”

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Types of Expert:

- Experts appointed by Applicant
  - To write Expert Reports on parts of the dossier
  - Ideally such experts are not company staff, especially not for safety and efficacy as it is difficult for them to remain critical and objective
  - For chemistry-pharmacy or manufacturing data, a company expert can be useful as nobody else would be able to have the knowledge needed...

- Experts appointed by Regulatory Authorities
  - They are typically brought in to help with dossier assessment, especially when resources or scarce or stretched.
  - In many agencies they are united in “scientific committee” of there is a scientific committee that coordinates the experts reviewing dossiers
• Experts appointed by Applicant from list of experts provided by Regulatory Authorities
  • E.g. Australia has list of “agreed” experts that are authorized to review dossiers, preparing them for the decision by the regulatory body
    ▪ Also to help alleviate resource issues
    ▪ **The Australian initiative**: allowing for independent - accredited by Authorities - Reviewer to be appointed and directly exchange with the applicant
      • APVMA appoints a number of accredited Scientific reviewers.
      • Applicant contacts directly with Scientific reviewers. Negotiates fee and timeline for review directly with reviewer.
      • Applicant submits Efficacy & Safety data to Reviewer. Output: Reviewer provides an Expert Report is provided directly to the applicant.
      • The applicant can use as part of a later full submission.
      • With this Expert report included in a submission, APVMA now only requires an ‘internal’ evaluation of the Part 8 (Efficacy & Safety) section.

*the Australian Pilot Efficacy Data Review Program: [Efficacy Contestability Pilot](www.Apvma.gov.au/node/18691)

• New approach in common assessment where agencies have split parts of the dossier: example Sheep claim on parasiticide co-assessed by Canada, Australia and New Zealand
1. How to avoid conflicts of interest:
   - Register of “trusted” experts
   - Ensure a declaration of interests is provided
     - Past employment history with industry
     - Current contacts with industry
   - Signed declaration of “absence of conflict of interest”

2. An expert report needs to be “critical” and facilitating
   - “nobody is perfect”
   - Typical content
     - Summary of all information
     - Critical evaluation
     - Opinion of expert if dossier contains sufficient and suitable data
     - CV and relationship with company

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3. Questions about Experts

- Are Expert Reports useful to Assessors?
  - How beneficial are “company” expert reports?
  - Can external academic experts or consultants facilitate your work?

- Is there any value in using an Expert Report from another country?

- Could trans-national organisations provide a list of suitable experts?

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4. Opportunities & Benefits of Harmonisation and Mutual Recognition

- Regulatory convergence, including alignment to international standards and guidelines is key

- **Regulatory convergence** / **harmonisation** goes beyond acceptance of VICH guidelines for study conduct

- It is the convergence of all regulatory aspects e.g. the framework itself - Initial approval, variations, renewals, pharmacovigilance etc. Realistic stepwise approach towards of the ultimate goal.

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4. Opportunities & Benefits of Harmonisation and Mutual Recognition

- Regional organisation including Mutual Recognition has been shown to bring value
- Most recent experiences: WAEMU/UEMOA, and East African Community (EAC)

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4.1 Opportunities & Benefits of Harmonisation and Mutual Recognition

The Benefits

Benefits to Applicants
• One dossier format
• One round of Q & A
• Improves predictability
• Simplifies administration of
  – Variations
  – Renewals

Benefits to Regulators
• Avoids duplication of assessment and inspections
• Builds trust and confidence between assessors and inspectors
• Common dossier format
• Helps less resourced agencies

for Customers/Farmers:
Opportunities to accelerate availability of good quality, safe and efficacious veterinary medicines

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Benefits to Applicants
• One dossier format
• One round of Q & A
• Improves predictability
• Simplifies administration of
  – Variations
  – Renewals

Benefits to Regulators
• Avoids duplication of assessment and inspections
• Builds trust and confidence between assessors and inspectors
• Common dossier format
• Newly formed or under resourced Regulatory Authorities benefit from experience of well established authorities. Therefore they can register products assessed by others as being of good quality safety and efficacy

for Customers/Farmers:
• Opportunities to accelerate availability of good quality, safe and efficacious veterinary medicines
4.2 Opportunities & Benefits of Harmonisation and Mutual Recognition

Existing Procedures:

- Other regions are interested in and/or starting to use a harmonised process.
  
  EAEU
  ASEAN
  SADC
  ZAZIBONA
  CAMEVET

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**EAEU = Eurasian Economic Union**
**ASEAN = Association of Southeast Asian Nations**
**SADC = Southern Africa Development Community**
**ZAZIBONA = Zambia, Zimbabwe, Botswana, Namibia**
**CAMEVET = north and south americas**

**EAC Mutual Recognition Procedure**

**The value of MRP:**

- Accelerates availability of new veterinary medicines.
- Avoids duplication of assessment.
- Builds trust between Regulators.
- Improves predictability.
- Removes multiple variations of dossier in different countries.
- The tools are now available.
- Other regions are interested in using the process.
4.3 Opportunities & Benefits of Harmonisation and Mutual Recognition

**Lessons learned:** What systems and tools are needed to enable mutual recognition? The 4 pillars approach:

- **Pillar 1:** **Common** set of technical registration requirements
- **Pillar 2:** Registration **Procedure:** MRP, define the how
- **Pillar 3:** **Political Will & Legal framework** to operate: existing supranational body/organization/forum & national laws to be adapted
- **Pillar 4:** **Implementation:** need for a coordinated, practical, hands-on and step-by-step guidance

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Pillar 1/ including GxP
2.0 Harmonisation and Mutual Recognition Procedures

- Is there any Mutual Recognition in the region at present?
- Do you accept assessments and/or inspections made by other countries?
- Do you accept clinical safety & efficacy data generated in other countries?

Examples from other Regions
- EU - 28 countries
- USA/Canada
- Africa
Thank you for your attention
Back-up slides for Workshop Session 4

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Example: Mutual Recognition Procedure (MRP) in East Africa

- MRP allows Marketing Authorisations to be issued without long delays
  - If no questions raised: <150 days to issue an Authorisations
  - If questions raised: <230 days to issue an Authorisations

- Two types of MRP:
  1. For new product applications
  2. For expansion of existing Marketing Authorisations

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Example: MRP in East Africa

1. One EAC Partner State acts as Reference Country (RC)
2. Concerned Countries (CCs) are other countries in which Marketing Authorisations will be sought
3. Coordination Group for Mutual Recognition (CGMR) is notified, MR-Coordinator prepares calendar for MRP
4. One week before <CLOCK START> Applicant sends dossier and Application Form to RC and National Authorities of CCs simultaneously.

Applicant → RC → CCs

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Example: MRP in East Africa

**CLOCK STARTS**

Step 1: Day 0 RC prepares Assessment Report (AR) 90 days
Step 2: Day 90 RC sends AR to CCs for review 30 days
Step 3: Day 120 If CC’s raise no objections, move to step 5
Step 4: If CCs raise additional questions on AR, RC and Applicant try to resolve them between days 120 - 180 60 days
Step 5: Day 180 If changes to packaging requested, Applicant sends revised labels/SPC to RC & CCs for approval 20 days
Step 6: Day 200 **CLOCK STOPS**

RC and CCs issue National Marketing Authorisations 30 days

- Total: if no questions – 150 days
- if questions raised – 230 days

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Back-up slides: EU Centralised procedure timelines

- D1: start
- D120: questions received
  - Clock stopped!
- D121: answers provided
- D210: CVMP Opinion
- D215 to D260: submission/validation of all translations of SPC and packaging elements
- 4 to 6 months later: European marketing authorisation obtained = Commission Decision
- Publication of EPAR: European Public Assessment report based on CVMP Opinion

**Overall duration** from first submission to EU approval: **12 - 18 months**

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The EU Mutual Recognition Procedure

**PHASE 1**: Application to first Member State (MS)
- **210 clock days***

**PHASE 2**: Update files and assessment report
- **90 days***

**PHASE 3**: Mutual recognition of selected MS
- **90 days***

**PHASE 4**: Issue of National Licences (potentially up to MSs)
- **30 days***

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**Steps**

1. **Applicant**
   - Dossier

2. **Member State 1** (Reference Member State)
   - Evaluation by national authority within **210 clock days***

3. **Registration MSs**

4. **Arbitration by CVMP (EMEA)**
   - Scientific Evaluation

5. **European Commission**
   - CVMP opinion

6. **Veterinary Standing Committee**

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**Timeframes**

- **90 clock days*** before November 2003
- **90 clock days*** (or up to 210 days if referred to the Council)
- **60 clock days*** before December 2003
- **15 days***
- **35 to 52 days***

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*clock days. If questions are sent to the applicant the “clock” is stopped, and it is only started again when answers have been received from the applicant.*
### Dossier Structures:

#### 1. Tabulated EU Vaccine Dossier Structure

<table>
<thead>
<tr>
<th>Part 1</th>
<th>Part 2</th>
<th>Part 3</th>
<th>Part 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Summary</strong></td>
<td><strong>Quality</strong></td>
<td><strong>Safety</strong></td>
<td><strong>Efficacy</strong></td>
</tr>
<tr>
<td>1.C.1 Quality</td>
<td>2.E: Controls on Finished Product</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.C.2 Safety</td>
<td>2.F: Batch consistency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.C.3 Efficacy</td>
<td>2.G: Stability</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.H: Other information</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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# Dossier Structures:

## 2. Tabulated EAC vaccine dossier structure

<table>
<thead>
<tr>
<th>Part 1 Administrative</th>
<th>Part 2 Quality</th>
<th>Part 3 Safety</th>
<th>Part 4 Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.B.2 Label and carton text</td>
<td>2.C: Control of SMs</td>
<td>3.B: Field Safety</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.E: Controls on Finished Product</td>
<td></td>
<td>Part 5 Bibliographical references</td>
</tr>
<tr>
<td></td>
<td>2.F: Batch consistency</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.G: Stability</td>
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