The implementation of a risk-based assessment approach by the South African Health Products Authority (SAHPRA)

Pharmaceutical Medicine

Lerato Moeti[1,2], Madira Litedu[1], Jacques Joubert[2]

[1]South African Health Products Regulatory Authority (SAHPRA), Pretoria, South Africa.

[2]University of the Western Cape, School of Pharmacy, Cape Town, South Africa.

Corresponding Author: jjoubert@uwc.ac.za

School of Pharmacy, University of the Western Cape, Robert Sobukwe Road, Bellville 7535, Cape Town, South Africa

1. Initial Quality Evaluation Report Template (All other dosage forms except steriles)
2. Initial Quality Evaluation Report Template (Sterile dosage forms)

PHARMACEUTICAL EVALUATION MANAGEMENT

PRE-REG UNIT EVALUATION REPORT FORMAT

HUMAN	VETERINARY	BIOLOGICAL	NCE	GENERIC	LINE EXT

Date of submission		
Application number	**Number**	
Product (proprietary) name	**Bold and indicate whether compendial**	
Approved name(s) (INN)	Names of APIs and indicate whether compendial	
Applicant		
FPP Manufacturer (plot number and address)		
API manufacturer (plot number and address)	Indicate whether used in the biobatch or/and development batch. If the biobatch and development batch are produced by different manufacturers add an additional row.	
BCS Class and polymorph (if applicable to the final product)		
APIMF number and version/CEP/WHO PQ API		
APIMF/CEP/WHO PQ API date (declaration that is current)		
Scheduling		
Dosage form	State whether immediate or modified release	
Description of dosage form		
Route of Administration		
Risk classification		
Stability of the API		
Date of commencement of study:	**Data available**	**Requested shelf life**
Stability of the Final Product		
Date of commencement of study:	**Data available**	**Requested shelf life**

Strength per unit dose	Include all APIs
Sterility of the final product	Indicate whether sterile or not, **if sterile use the sterile evaluation template**
Packaging	
Country of origin	Formulation development
Foreign registration	Countries where registered

TECHNICAL SCREENING: The same template to be used for technical screening. The screener to state critical deficiencies found. The information to be populated by the screener are in black text highlighted in yellow. Once the information has been completed, the screener should remove the yellow highlight. The screener's report should be shared with the initial evaluator so that the populated information can be reproduced.

Key:
Red: Initial screener conclusions
Blue: Second screener conclusions.
Red: First reviewer's conclusions.
Comments pane: peer reviewer's comments and discussions
Green: peer review meeting conclusions.
Queries to the applicant by the screener and initial evaluator: Red text highlighted in yellow

MODULE 1

1 General comments on the dossier

2 Administrative/legal (Module 1)

2.1 Labelling (PI, PIL and Label) (Module 1.3)

2.1.1 Name of the product: Ensure this is the same as in the application form.

2.1.2 Qualitative and Quantitative Composition: Ensure this is the same as in the application form and **3.2.P.1**

2.1.3 Pharmaceutical Form: Ensure this is the same as in the application form and **3.2.P.7**

2.1.4 Pharmaceutical Particulars: Ensure the list of excipients is the same as in section **3.2.P.1**

2.1.5 Shelf life: Ensure this is the same as in section **3.2.P.8**

2.1.6 Special precautions for storage: Ensure this is the same as in the application form and **3.2.P.8**

2.1.7 Nature and contents of container: Ensure this is the same as in section **3.2.P.7**

2.1.8 Posology: State the recommended dose, this is important in order to determine the identification and qualification thresholds for related impurities [refer to ICH Q3A (API) and Q3C (Final product). The thresholds are based on maximum daily dose (MDD) and the duration of treatment (acute vs chronic).

2.2 Good manufacturing practice (Module 1.7)

2.2.1 Release API, IPIs
2.2.2 Release FPRC/FPRR

2.3 Foreign regulatory status

2.3.1 Relevant for reliance pathway. Presence of the reports will be checked at screening.

3 MODULE 2 – CTD SUMMARIES

3.1 Quality Overall Summary - Introduction

3.1.1 (No comments on QOS). Presence will be checked at screening.

MODULE 3 - QUALITY

4 ACTIVE PHARMACEUTICAL INGREDIENT (Module 3.2.S)

4.1 Active Pharmaceutical Ingredient no 1 [Manufacturer 1]

4.1.1 General Information should be confirmed by the screener in order to populate the table above.

Include Structure, molecular formula and few details of the API for completeness of the report.

4.1.2 Sources(s) or Manufacturer of the API should be confirmed by the screener.

4.1.3 Method of Synthesis:
3.2.S.2.2 Assess the appropriateness of the method of synthesis and acceptability of Starting material

3.2.S.2.2 Assessment of nitrosamines should be conducted to confirm potential formation (all products):
The above-mentioned product/s was/were assessed for the presence of N-nitrosamine impurities. The evaluator finds risk assessment acceptable. The evaluator's risk assessment demonstrated that there is no risk of nitrosamines. This is considered acceptable and therefore qualifies the product as safe. OR

The applicant has not provided a risk assessment to SAHPRA as this is not currently available. The applicant has therefore provided a commitment to submit such information as soon as it becomes available. OR

N-nitrosamine impurities are of concern as they are probable human carcinogens. Based on the reaction conditions observed which show potential of formation of nitrosamine impurities it is requested that the possibility of nitrosamine being present in the API be evaluated. OR

A CEP/CPQ has been submitted, therefore the nitrosamine investigation is currently underway and will be concluded by EDQM/WHOPQ.

4.1.4 Degradation Products, Impurities and Related Substances: Check if the proposed specifications are not according to ICH Q3A and residual solvents, elemental impurities, nitrosamines, mutagenic impurities are not included.

4.1.5 Specifications: Ensure that the reference number, version, date are included and also signed. These must be included in the report as indicated in the example below. Confirm compliance with the claimed pharmacopoieal monograph. Ensure the proposed specifications are according to ICH Q3A if not evaluate the impurity section.
The approved FPP manufacturer's API specification:

API manufacturer's API specifications:

4.1.6 Validation of methods: Evaluate for the sterile and non-pharmacopoeial APIs and write a summary of the findings.

4.1.7 Stability protocol, data and retest period: Evaluate data and approve the retest period as the paragraph below. The screener should check this information so they could populate the table above.

A retest period of …. months is approved for API manufactured by ….API manufacturer…. when packed in an inner HMHDPE and outer black polyethene bags enclosed in a fibre drum and stored at or below 30 °C.

4.2 Active Pharmaceutical Ingredient no 1 [Manufacturer 1]

4.2.1 xxx
4.2.2 Check 3.2.R.4

4.3 Active Pharmaceutical Ingredient no 2 [Manufacturer 1]

4.3.1 xxx

5 PHARMACEUTICAL PRODUCT (Module 3.2.P)

5.1 Description and Composition of the FPP (Module 3.2.P.1)

5.1.1 INN or approved names, and/or chemical names of all APIs, and polymorph (if relevant to the final formulation).
5.1.2 Names and quantities to correspond with PI/PIL/Label
5.1.3 Purpose of each component
5.1.4 Potency of active
5.1.5 Overages and reasons
5.1.6 Total quantity of unit dose

5.2 Pharmaceutical development (Module 3.2.P.2)

5.2.1 Formulation Development: Assess for the high risk dosage forms
5.2.2 Production History: Assess for the high risk dosage forms
5.2.3 Final product specifications: Assess for the high risk dosage forms
5.2.4 Stability, etc. See stability guideline

5.3 Manufacture (Module 3.2.P.3)

A. [Manufacturer 1]**:**

5.3.1 Batch formula
5.3.2 Manufacturing Process: Assess this in conjunction with the 3.2.R.7 Executed and blank BMRs
5.3.3 Packaging Process: Important for high risks dosage forms
5.3.4 In-Process Controls: Important for high risks dosage forms

5.3.5 Process Validation: Important for high risks dosage forms

B. [Manufacturer 2]:

5.3.6 Check data in 3.2.P.2 and 1.5.2.3 and 3.2.R.1.4

5.4 Control of Inactive Pharmaceutical Ingredients (Module 3.2.P.4): Important for high risks dosage forms

5.4.1 Specifications and limits
5.4.2 Test procedures
5.4.3 Check module 1.7.4
5.4.4 Source (human/animal?)/ TSE/BSE certifications

5.5 Control of the Pharmaceutical Product (Module 3.2.P.5)

5.5.1 Specifications: Ensure that the reference number, version, date are included and also signed. These must be included in the report as indicated in the example below. Confirm compliance with the claimed pharmacopoieal monograph. Ensure the proposed specifications are according to ICH Q3C. If not according to ICH guidance check the impurity profile of the product

5 mg Specification number and version
Release:
Shelf-life:
10 mg Specification number and version
Release:
Shelf-life:

5.5.2 Test Procedures: Important for high risks dosage forms
5.5.3 Validation of Analytical Methods: Important for high risks dosage forms
5.5.4 Batch analysis: Important for high risks dosage forms

5.6 Container closure system (Module 3.2.P.7). Important for high risk dosage form

5.6.1 Specifications and limits
5.6.2 Test procedures

5.7 Stability (Module 3.2.P.8)

5.7.1 Stability Program
5.7.2 Stability Data
5.7.3 Shelf-life. This is important for the screener to populate the table above
5.7.4 Preserving Ability (if applicable)

A shelf life of …. months is approved for …….(product)…. manufactured by ….(FPP manufacturer)….with API manufactured by ….. (API manufacturer)…., when packed in … and stored at or below 30 °C.

6 Regional information (Module 3.2.R)

6.1 Certificates of Suitability CEPs/ WHO CPQ

6.1.1 Include the number and validity thereof in the report

EVALUATORS

Full name	Signature	Date
1 Screener:		
2 Second screener		
3 Evaluator		
4 Peer reviewer (Group Meeting)		

PHARMACEUTICAL EVALUATION MANAGEMENT

PRE-REG UNIT EVALUATION REPORT - INJECTIONS

HUMAN	VETERINARY	NCE/GENERIC	LINE EXT

Date of submission					
Application number					
Product (proprietary) name					
Approved name(s) (INNM)					
Applicant					
Manufacturer (plot number and address)					
API manufacturer (plot number and address)					
APIMF number and version/CEP/WHO PQ API					
APIMF/CEP/WHO PQ API date (declaration that is current)					
Scheduling					
Dosage form	Solution/Concentrate for dilution	Lyophilized Powder for solution	Powder for solution or suspension	Suspension for injection	Emulsion
Volume of Injection	(≥ 100 ml)			(<100 ml)	
Single dose/Multi dose	Single dose			Multi dose	
Sterilisation method	Autoclaving/Heat	Sterile filtration	Aseptic processing	Other	
Dosage					
Risk classification					
Stability of the API					

Date of commencement of study:	**Data available**		**Requested shelf life**	
Stability of the Final Product				
Date of commencement of study:	**Data available**		**Requested shelf life**	
Strength per unit dose				
Description of dosage form				
Route of administration	IV	IM	IV/IM/SC	Other (Intrathecal)
Packaging				
Country of origin				
Foreign registration				

TECHNICAL SCREENING: The same template to be used for technical screening. The screener to state critical deficiencies found. The information to be populated by the screener are in black text highlighted in yellow. Once the information has been completed, the screener should remove the yellow highlight. The screener's report should be shared with the initial evaluator so that the populated information can be reproduced.

Key:
Red: Initial screener conclusions
Blue: Second screener conclusions.
Red: First reviewer's conclusions.
Comments pane: peer reviewer's comments and discussions
Green: peer review meeting conclusions.
Queries to the applicant by the screener and initial evaluator: Red text highlighted in yellow

1. General

2. Module 1.3 Labeling (PI, PIL and label)

2.1. Are reconstitution or dilution required (*Concentrate for dilution/Lyophilized powder/powder*)?

If so check the instructions in "*Dosage and Directions for use*" for complete instructions including diluents and diluent - volume.

Comments:

2.2. In "*Dosage and Directions for use*" check compatibility information with recommended IV solutions and check whether this has been investigated either in 3.2.P.2 or 3.2.P.8.

Comments:

2.3. Confirm the stability information of the reconstituted/diluted product ("*Dosage and Directions for use" and "Storage instructions").*

2.4. Check that a statement is included for the reconstituted/diluted product to be used immediately and/or include the following statement (unless it is a multi-dose injection and preservative efficacy has been established)

"From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless reconstitution/ dilution has taken place in controlled and validated aseptic conditions"

Comments:

2.5. For single dose injections, indicate on the labels that it is for single use and that any unused portion should be discarded.
For multi-dose injections and eye drops indicate that it should not be used for the validated period (normally 30 days) after first opening the container

Comments:

2.6 Name of the product: Ensure this is the same as in the application form.

2.7 Qualitative and Quantitative Composition: Ensure this is the same as in the application form and **3.2.P.1**

2.8 Pharmaceutical Form: Ensure this is the same as in the application form and **3.2.P.7**

2.9 Pharmaceutical Particulars: Ensure the list of excipients is the same as in section **3.2.P.1**

2.10 Shelf life: Ensure this is the same as in section **3.2.P.8**

2.11 Special precautions for storage: Ensure this is the same as in the application form and **3.2.P.8**

2.12 Nature and contents of container: Ensure this is the same as in section **3.2.P.7**

2.13 Posology: State the recommended dose, this is important in order to determine the identification and qualification thresholds for related impurities [refer to ICH Q3A (API) and Q3C (Final product). The thresholds are based on maximum daily dose (MDD) and the duration of treatment (acute vs chronic).

3. Module 1.7 Good manufacturing practice

3.1. Release API, IPIs

Comment:

3.2. Release FPRC/FPRR

Comment:

4 Module 1.10 Foreign regulatory status

4.1 Relevant for reliance pathway. Presence of the reports will be checked at screening.

5 Module 2 CTD Summaries

5.1 This should reflect a summary of the essential information as indicated in 3.2.P.2.

Comment:

6 Module 3.2.S

6.1 The required information is the same as for all products except when the API is sterile and/or blended with another API or IPIs. See Quality and bioequivalence guideline 3.2.S.2.2 "Other relevant aspects, e.g. preparation of sterile material (full description of aseptic or sterilisation process including conditions), if there is no further sterilisation of the FPP". See also attached Policy regarding the Manufacture of Blended Powders for Injection.

6.2 Microbial purity and Bacterial endotoxins should be included as a specification when the API is used for the manufacture of sterile products. This is normally not part of the specifications for the API by the API manufacturers or pharmacopoeial specifications and should be added.

6.3 Method of Synthesis: 3.2.S.2.2 Assess the appropriateness of the method of synthesis and acceptability of Starting material

3.2.S.2.2 Assessment of nitrosamines should be conducted to confirm potential formation (all products):

The above-mentioned product/s was/were assessed for the presence of N-nitrosamine impurities. The evaluator finds risk assessment acceptable. The evaluator's risk assessment demonstrated that there is no risk of nitrosamines. This is considered acceptable and therefore qualifies the product as safe. OR

The applicant has not provided a risk assessment to SAHPRA as this is not currently available. The applicant has therefore provided a commitment to submit such information as soon as it becomes available. OR

N-nitrosamine impurities are of concern as they are probable human carcinogens. Based on the reaction conditions observed which show potential of formation of nitrosamine impurities it is requested that the possibility of nitrosamine being present in the API be evaluated. OR

A CEP/CPQ has been submitted, therefore the nitrosamine investigation is currently underway and will be concluded by EDQM/WHOPQ.

6.4 Degradation Products, Impurities and Related Substances: Check if the proposed specifications are not according to ICH Q3A and residual solvents, elemental impurities, nitrosamines, mutagenic impurities are not included.

6.5 Specifications: Ensure that the reference number, version, date are included and also signed. These must be included in the report as indicated in the example below. Confirm compliance with the claimed pharmacopoieal monograph. Ensure the proposed specifications are according to ICH Q3A if not evaluate the impurity section.
The approved FPP manufacturer's API specification:
The approved API manufacturer's API specification:

6.6 Validation of methods: Evaluate for the sterile APIs and write a summary of the findings.

6.7 Stability protocol, data and retest period: Evaluate data and approve the retest period as the paragraph below. The screener should check this information so they could populate the table above.

6.8 A retest period of …. months is approved for API manufactured by ….API manufacturer…. when packed in …and stored at or below 30 °C.

7 **Module 3.2.P.1** Description and Composition of the FPP

7.1 If Nitrogen is used as a pressure source for filtration, it must be included in the unitary and batch formula and indicated in a footnote that it is not present in the final product. It must be controlled in 3.2.P.4.

7.2 INN or approved names, and/or chemical names of all APIs, and polymorph (if relevant to the final formulation).
7.3 Names and quantities to correspond with PI/PIL/Label

7.4 Purpose of each component
7.5 Potency of active
7.6 Overages and reasons
7.7 Total quantity of unit dose

8 **Module 3.2.P.2** Pharmaceutical development

8.1 The information in this module is very important and the following should be adhered to.

Formulation Development: Assess for the high-risk dosage forms such as steriles and metered dose inhalations.
Production History: Assess for the high-risk dosage forms
Final product specifications: Assess for the high-risk dosage forms
Stability, etc. See stability guideline

8.2 Of specific importance to injections are the physical form of the injection, the route of administration (IV,IM,SC or other) and the volume of the injection. The primary concern is:

- Sterility and maintanance of sterility of the product
    - Sterilisation method
    - Container-closure integrity
    - Preservative efficacy (multi-dose injections)
- Bacterial endotoxins
    - Control of the APIs and IPIs (specifications)
    - Depyrogenation of glass containers
- Physiological acceptability
    - pH
    - isotonicity
    - partuculate matter
    - viscosity
    - density

Comments:

All these aspects should be addressed during Formulation development and Manufacturing process development where appropriate to the dosage form, volume of injection and route of administration, e.g.:

- The choice of sterilization method must be investigated according to the decision tree for the choice of sterilization methods. Autoclaving is the method of choice. Any other method should be motivated.
- Container-closure integrity should always be validated
- The solubility of the API and the influence of pH on the solubility in water or the chosen solvent should be investigated for APIs of poor solubility.
- Compatibility of the product with production equipment, filter-media, and diluents for IV administration and container components should be addressed.
- Possible precipitation of poorly soluble APIs during storage and after administration should be addressed
- Viscosity is essential for IM injections
- Density and viscosity is important in injections in the spinal column e.g. epidural injections.
- Droplet size distribution is of major concern for IV oil-in-water emulsions(propofol).
- Preservative efficacy in multi-dose containers must be addressed; however, often this is being addressed in 3.2.P.8.
- In-use stability of reconstituted or diluted injections must be addressed.
- For Lyophilized injections the development and validation of the lyophilisation cycle is important.
- When a product is sterilized by filtration, the APIs and IPIs need not be sterile but should have a very low bioburden and should be endotoxin-free. All steps after filtration should take place in a Class A area with a Class B background.
- For products such as powders, all APIs and IPIs should be sterile and the whole manufacturing process should take place in a Class A/B area.

9 **Module 3.2.P.3** Manufacture

9.1 The Quality and Bioequivalence guideline **3.2.P.3.3** specifies that the following should be submitted:

- A comprehensive flow diagram, detailing the various stages of manufacturing - and
- A comprehensive description of the manufacturing procedures detailing the various stages of manufacturing – derived from the master manufacturing records.

9.2 A. [Manufacturer 1]:

Manufacturing Process: Assess in conjunction with the BMRs and 3.2.P.3.5 process validation.

Packaging Process: Important for high risks dosage forms

In-Process Controls: Important for high risks dosage forms

Process Validation: Assess in conjunction with 3.2.P.3.3

B. [Manufacturer 2]:

Check data in 3.2.P.2 and 1.5.2.3 and 3.2.R.1.4

Comments:

Depending on the nature of the injection and method of sterilization, the description should be **both comprehensive but concise** and the description or the flow diagram and preferably both should indicate the grades of clean areas of the various areas of production; methods and conditions of sterilisation/depyrogenation (time/temperature) of manufacturing components and filter media; the pressure source used for filtration and it's method of sterilisation; the final method of sterilisation; in-process controls such as bioburden testing and acceptance criteria,; filter integrity testing; the maximum validated processing times (holding times) for the various stages of manufacturing.

9.3 Over and above the requirement of 3.2.P.3.5 and depending on the product, container-closure system and method of sterilization, the following should be submitted:

- Process validation report or protocol,
- validation report of aseptic processing by media fill
- summary report of the validation of the final sterilization process (including load patterns)
- summary report on the depyrogenation process of glass containers
- summary report on autoclaving of production equipment and filter media
- report on the validation of the maximum processing times of the various stages of manufacturing (chemical/physical and microbiological)

Comments:

10 Module 3.2.P.4 Control of Excipients - Important for high risks

10.1 Provide specifications and control procedures for the Nitrogen used as pressure source for filtration if applicable.

11 Module 3.2.P.5 Control of Pharmaceutical Product

The guidance in the assessors guide 3.2.P.5 should be followed.

11.1 3.2.P.5.1 Specifications for in-process controls must be included. If the in-process controls are submitted in 3.2.P.3.3 a cross will suffice.

11.2 3.2.P.5.1 Visible particulate matter must be specified as a final release criteria or in-process control specification in addition to sub-visible particulate matter.

11.3 Evaluation of FPP intermediates for parenterals (powder blends) should also include homogeneity, and FPP intermediate sterile powders should also include evaluation of sterility and bacterial endotoxin testing (BET).

11.4 The preservative efficacy of relevant dosage forms and/or presentations, e.g. multi-dose vials, eye drops should be specified in 3.2.P.5.1 and presented in 3.2.P.8. However, once established for **the lowest limit of preservative content** specification, it is not a routine batch test requirement.

11.5 For Bacterial endotoxin determination the validation data required by the USP / BP/ Ph Eur, should be submitted.

11.6 Specifications: Ensure that the reference number, version, date are included and also signed. These must be included in the report as indicated in the example below. Confirm compliance with the claimed pharmacopoieal monograph. Ensure the proposed specifications are according to ICH Q3C. If not according to ICH guidance check the impurity profile of the product

11.7 Test Procedures: Important for high risks dosage forms

11.8 Validation of Analytical Methods: Important for high risks dosage forms

Comments:

12 **Module 3.2.P.7** Container closure system

12.2 For Injections packed in **glass containers** the Type of glass must be specified and compliance with pharmacopoeial specifications must be confirmed.

12.3 Specifications for **rubber caps** must comply with pharmacopoeial requirements and compatibility with the formulations must be proven either here or in 3.2.P.2.

12.4 For injections packed in **plastic containers** the type and formulation of the plastic material must be specified, it must comply with pharmacopoeial specifications and CPMP-QWP-4359-03 including sorption studies, migration studies and toxicological information.

12.5 The container-closure integrity must be validated unlesss it has already been done in 3.2.P.2.

12.6 Specifications and limits

12.7 Test procedures

Comments:

13 **Module 3.2.P.8** Stability

13.2 Follow the general guidance of the P&A Guideline (2.25_PA_CTD,3.2.P.8) and the stability guideline (2.05 Stability Feb11 v6).

13.2 Injections packed in glass vials with rubber caps must be stored upright and inverted to test for any interaction of the product with the rubber caps (sorption or extraction).

13.3 Injections packed in semi-permeable containers (Plastic containers) must be tested for water loss at low humidity.

13.4 The protocol and results of preservative efficacy testing where relevant must be provided.

13.5 Where relevant specifications and results for preservative concentration and antioxidant concentration must also be included.

13.6 Where relevant in-use stability must be tested.

13.7 Photo stability study must be presented unless it has been done in 3.2.P.2.

13.8 The compatibility with the listed IV solutions under *"Dosage and Directions for use*" in the PI must be reported on.

13.9 Stability Program

13.10 Stability Data

13.11 Shelf-life. This is important for the screener to populate the table above

13.11 Preserving Ability (if applicable)

A shelf life of …. months is approved for …….(product)…. manufactured by ….(FPP manufacturer)….with API manufactured by ….. (API manufacturer)…., when packed in …and stored at or below 30 °C.

Comments:

14 **Module 3.2.R** Regional information

14.1 Pharmaceutical and Biological availability (3.2.R.1.4.2)

Exemption must be requested from submitting a proof of equivalence study in Module 3.2.R.1 based on the fact that the formulation is essentially the same as innovator product and contains the same active ingredient in the same molar concentration as the reference product. Essential similarity to the innovator product must be proven (Sometimes proven in 3.2.P.2). Injections in solution intended for IV or IM administration are normally exempt.

Comments:

15 Certificates of Suitability CEPs/ WHO CPQ

15.1 Include the number and validity thereof in the report.

EVALUATORS

Full name	**Signature**	**Date**
1 Screener:		
2 Second screener		
3 Evaluator		
4 Peer reviewer (Group Meeting)		