TEMPLATE FOR PROVIDING COMMENT ON THE DRAFT GENERAL REGULATIONS MADE IN TERMS OF THE MEDICINES AND RELATED SUBSTANCES ACT, 1965 (Act 101 of 1965)

Name of Organisation / Individual:	Innovative Pharmaceutical Association South Africa (IPASA)
Date of submission:	20 April 2017

Comment no.	Pg no.	Regulation, subregulation or paragraph			Comment and Rationale	Proposed Revised Text **Bold underlined –** additions **[square brackets bold] –** deletions
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THROUGHOUT THE REGULATIONS						
1					Change the wording from Medicines Control Council to Authority. Some instances: Pg 53 Reg 8(1)cc(ii), Pg 57 Reg 9(2) t(ii) and Pg 58 Reg 10(2) n(ii) Pg 94 Reg 41 (1) w(ii)	evaluated by the **[Medicines Control Council]** **Authority**
2					Professional information to change to Prescribing Information Pg 55 Reg 9(1)	**[Professional Information]** **Prescribing Information**
SPECIFIC COMMENTS						
3	Pg 43				List of contents No 6: should change wording to state that the applications 'approved' for registration are published.	6. Particulars to be published in the Gazette in respect of applications **[received]** **approved** for registration in terms of section 14(3)
4	Pg 46				Distributor - definition to be included This definition has been flagged in the Act as an omission and needs very careful consideration to avoid unintended consequences. It is not the same as for medical devices.	**"Distributor" means a person who is licensed in terms of Section 22C of the Act to distribute medicines or scheduled substances on behalf of a manufacturer or a primary importer, or to purchase and distribute, the finished product only into the retail sector and only to any**

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						person who may lawfully possess such medicine or scheduled substance.
5	Pg 47				Manufacturer – definition to be included	**"Manufacturer" means a person manufacturing a medicine and includes a manufacturing pharmacy"**
6	Pg 47				Professional information to remain Prescribing Information *throughout the regulations; keep the definition unchanged*	**['Professional Information'] 'Prescribing information'**
7	Pg 47				In light of the definition for Prescribing Information above, there should be a definition for Product / Patient Information Leaflet. Please refer comment number 23. Reference is also made to align Pg 57 Reg 10 Header 'Consumer information'	**"Product / Patient Information Leaflet" means the information pertaining to a medicine, written in patient-intelligible language lay terms for the patient as provided in Regulation 10.**
8	Pg 47				Sugar - definition to be included *Note, if the sugar definition **is** included in the recommendations then the Guideline itself will have to be updated to modify the current statement – "There is no reference to "sugar" in the Act itself, and no definition of "sugar" in the regulations."*	**"Sugar" means any of a class of natural, water soluble crystalline carbohydrates, of relatively low molecular weight, and typically having a sweet taste, and classified as either monosaccharides, disaccharides, trisaccharides etc. depending on the polymeric composition. Examples include sucrose, fructose, glucose, lactose and related alcohols such as sorbitol, mannitol, and xylitol.**
9	Pg 49	5	1		Positive comment - inclusion of timelines for each step of the regulatory assessment. Current regulation only speaks to receipt of application and screening but not for evaluation. Recommendation to include timelines for the end-to-end process. We recognise these Regulations apply to medicines but wish	The Authority shall **within 20 working days [as soon as practically possible]** inform any applicant of the application number and receipt of an application for the registration of a medicine, medical device and IVD;

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					to emphasis a similar need for Medical Devices and IVDs	
10	Pg 49	5	2		A specific time frame is required.	The Authority shall **within 20 working days [as soon as practically possible after] from the date of** receipt of the application by the Authority inform any applicant in respect of any application referred to in subregulation (1) on the acceptance of the application for evaluation
11	Pg 49	5	3		Specific time frame is required.	**Add 5(3)** **(i) The Authority shall, within 12 months from the date of receipt of an application for an interchangeable multisource medicine or biosimilar medicine or line extension by the Authority, or within 18 months from the date of receipt of an application for a new chemical entity or new biological medicine by the Authority, make a final decision with regard to the application and inform the applicant of such decision.** **(ii) The response time from the applicant is excluded from the time frames stipulated in subregulation (3)(i).**
12	Pg 49	5	4		A time frame is required for amendments/variations requiring approval. This will then include P&A Type C and any clinical amendments i.e. new indications or changes to approved indications, amendments that would result in a change in the balance of clinical benefit to risk ratio of a medicine. The Professional Information amendment guideline will then	**Add 5(4)** **(i) The Authority shall notify the applicant of a decision to approve, reject or request clarification or further information for variation / amendments requiring the approval within 60 working days from receipt of the application and evaluation fee.** **(ii) The Authority shall notify the applicant of a decision**

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					provide details of what requires approval but it will not be all amendments.	**to approve, reject of request clarification for responses to amendments within 20 working days from receipt of a response.** **(iii) If the Authority has not notified the applicant about the approval or rejection of an amendment application within:** - **60 working days of receipt of the application and evaluation fee, or** - **20 working days of receipt of a response, and** - **a request for further clarification or information has not been sent to the Applicant, then these amendments will be deemed to have been approved.**
13	Pg 49	5	5		A time frame is required for the issuing of certificate of registration.	**Add 5(5)** **Subject to a decision to approve an application as per subregulations (3) and (4), the certificate of registration or amended certificate of registration, where relevant, will be issued within 10 working days from the date of the decision.**
14	Pg 49	5	6		Section 2B(2) in the Act states that the Regulator has a discretion (the word "may" is used) to: 1) liaise with other authorities, exchange and receive information and 2) cooperate with any authority.	**Add 5(6)** **For applications that have been reviewed by recognised regulatory authorities, the authority may utilize the review reports from these authorities.**

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15	Pg 49	6	Head		Align to device Regulations Applications received are still confidential and should not be published Particulars to be published in the gazette in respect of applications **received** for registration referred to in Section 14(3)	Particulars to be published in the gazette in respect of applications **[received] approved** for registration referred to in Section 14(3)
16	Pg 49	6		d, g, h	Change 'the name of the person' to 'the entity / applicant' (and then to include associated definitions above)	**[name of the person] entity / applicant**
17	Pg 50	7	2	e	This section should include documentary proof of consent from the patent holder, proposal to add an additional stipulation.	Add 2 e **(vi) that the patent holder has given their consent for the importation**
18	Pg 50	7	3		This section to include wording that informs the patent holder of the issue of the permit, proposal to add an additional stipulation.	Add 3 **(d) shall inform the patent holder that a permit has been issued**
19	Pg 51	7	6	a	…in the public interest'. This term is vague and can be interpreted in multiple ways. The criteria that constitute public interest should be stated; recommend the following be included in the definitions.	**Add to definitions** **"Public Interest" means the welfare of the public as compared to the welfare of a private individual or company. All of society has a stake in this interest and the promotion of and protection of the general public is recognized.**
20	Pg 52	8	1	h (i)	Sugar Guideline to be finalised	
21	Pg 52	8	1	h (iii)	Sweetener not included in the Sugar Guideline	
22	Pg 52	8	1	p	Barcode: A barcode is issued based on company-specific logistical procedures and not as determined by the Authority.	(p) a barcode suitable for the identification and tracking of medication **[as determined by the Authority]**

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					The barcode details should not be a requirement for the regulatory dossier, even though it is ultimately on the immediate container.	
23	Pg 53	8	1	aa & bb	Seek clarification on the intended need for aa and bb Preference not to have the category (aa) and pharmacological classification (bb) on the container label	Propose to remove **[bb]** as a requirement
24	Pg 53	8	2		Positive comment – We welcome the inclusion of this option - harmonisation labelling requirements with other health authorities	
25	Pg 54	3	a-e		To be corrected and aligned with the current numbering of the proposed 8(1) - (w) not to be listed as a requirement under (c). Need for pharmacological action (bb) questioned on the immediate container, due to the frequent problem of space constraints. Preference not to have the pharmacological classification (bb) on the immediate container label. Requirements for medicines packaged in blister or similar packaging to include (q) – the name of the HCR, this has been omitted.	(a) in the case of medicines intended for administration by injection and having a total volume not exceeding 5 ml, the particulars referred to in subregulation (1)(b), (e), (m), (n), (o), (p) and **(q) [(bb)]**; (b) in the case of an ointment, cream, gel or powder having a net mass not exceeding 10 grams, the particulars referred to in subregulation (1)(b), (c), (e), (f), (n), (o), (p), (x) and **(q) [(bb)]**; (c) in the case of liquid, solution or suspension having a total volume of more than 1 ml, but not exceeding 15 ml, the particulars referred to in subregulation (1)(b), (c), (d), (e), (n), **[(w)]**, (o), (p), (x) and **(q) [(bb)]**; (d) in the case of a liquid, solution or suspension having a total volume not exceeding 1 ml, the particulars referred to in sub

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						regulation (1)(b), (n) and **(g) [(bb)]**; and (e) in the case of a medicine packed in blister or similar packaging, the particulars referred to in subregulation (1)(b), (n), (o), (p) and **(g) [(bb)]**, repeated as frequently as is practicable.
26	Pg 55	9	1		Please refer comment number 6 above. Professional information to change to Prescribing Information	**[Professional Information] Prescribing Information**
27	Pg 55	9	1	a (ii)	Positive comment - we welcome the move to electronic PIs	
28	Pg 55	9	1	a (ii)	Please refer comment number 7 above, for inclusion of definitions on Pg 47. Consistency required with regard to Patient Information Leaflet or Consumer Information; we recommend Product / Patient Information Leaflet.	**[Professional Information] Prescribing Information**
29	Pg 55	9	2	e	Align wording to currently used terminology, pharmacokinetics and pharmacodynamics is inconsistent with current terminology	pharmacological action and, where applicable, under a sub-heading **[pharmacokinetics] pharmacokinetic properties, [pharmacodynamics] pharmacodynamic properties**; summary of pre-clinical or clinical studies
30	Pg 56	9	2	j	Align with SmPC terminology; replace the term Human reproduction	**[Human reproduction] fertility, pregnancy and lactation**
31	Pg 56	9	2	s	Positive comment - happy to see this inclusion, as one can see when something was updated recently	
32	Pg 56	9	2	t(i)	Health supplements are noted as a sub-category of complementary medicines as per Regulation 25A and thus	in the case of complementary medicine -

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					this needs to be aligned to reflect this to avoid confusion.	(i) a statement identifying the **[discipline] sub-category,** where relevant;
33	Pg 57	10			Align to comment number 7 above Header 'Consumer Information' to remain 'Product / Patient Information Leaflet'. Essential to remain aligned with terminology used across other health authorities	**[Consumer Information] Product / Patient Information Leaflet**
34	Pg 58	10	2	d	Suggest reword to align with PI	the approved indications **for [and]** use
35	Pg 58	10	2	e (ii)	Suggest reword to align with PI	**[precautions and warnings] warnings and special precautions**
36	Pg 58	10	2	e (v)	All general statements that impact the current guidelines need to be reviewed and the associated guidelines aligned	
37	Pg 58	10	2	m	Align to wording in 9 (2) s which reads: date of publication of the professional information which is the date of the most recent amendment to the professional information as approved by the Authority as well as the date of registration:	Date of publication of the patient **[/product]** information leaflet which is the date of most recent amendment to the patient **[/product]** information leaflet as approved by the Authority as approved by the Authority **as well as the date of registration**
38	Pg 59	10	3		Positive comment - electronic format in other official languages	
39	Pg 59	10	4		Positive comment - include additional information	
40	Pg 59	10	5		Positive comment - allows for deviations	

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41	Pg 59	10	6		Positive comment - welcome	
42	Pg 59	10	6		Incorrect numbering - renumber second 6 to 7	**[(6)] (7)** The requirements of subregulation (1) shall not apply to any medicine sold in accordance with section 14(4) of the Act.
43	Pg 59	11	1		Ensure alignment with POPI Act and the implication wrt protecting the information recorded	
44	Pg 59	15	1	g	Typographical error	(g) purpose for such **important [importation]** or exportation.
45	Pg 66	16	2	a	Typographical include an 'or'	…a Scheduled substance; **or**
46	Pg 72	20	3		The reference is incorrect; currently refers to subregulation (2) only, it should refer to both subregulation 1 and 2	(3) A licence referred to in **subregulation (1) or** subregulation (2) which has expired may be renewed upon application to the Authority.
47	Pg 73	21	5		The reference is incorrect; should read subregulation 2 not 3	(5) The Minister shall, within 30 days of receipt of the reasons referred to in subregulation **(2) [3]**, confirm, set aside or vary the decision of the Director -General.
48	Pg 74	22	3	c	"Country of origin" refers to the country where development took place, according to ***2.01_General_information_Jul12_v8***. GMP certificates and manufacturing licences are included in our application, but are not specifically generated from the HA of the medicine's country of origin. According to the guidelines, the GMP certificates can be issued by any authority with which the MCC aligns itself? It is important that the Guidelines are aligned with the Regulations.	
49	Pg 75	22	4		Positive comment - only English required	
50	Pg 75	22	5	(b)(v)	Registration status outside the Republic is currently not a	Country of origin **[and registration status outside the**

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					requirement on the application for registration form. This information is already required in Module 1.10 of the ZACTD and this would be duplication	**Republic]**;
51	Pg 76	22	10		Align with current regulations and remove this section 'An application referred to in subregulation (1) shall be accompanied by three samples of such medicine subject to the provisions of regulation 12(2)'. This is covered in the general information guidelines (2.01) – one sample of smallest pack size.	**[(10) An application referred to in subregulation (1) shall be accompanied by three samples of such medicine subject to the provisions of regulation 12(2)]**
52	Pg 77	23A	1		Positive comment - permitting transfer of information	
53	Pg 78	24	2B		Positive comment - allowing an affidavit for lost certificates	
54	Pg 79	28	1	c	Positive comment - allowing electronic prescriptions	
55	Pg 81	28A	3		Typographical error; include a space	**[medicineshall] <u>medicine shall</u>**
56	Pg 82	29	1	b(i)	Typographic error; correct spelling	**[reparation] <u>preparation</u>**
57	Pg 82	29	3	b	There should be a space between 10 and %	
58	Pg 82	29	3	d	There should be a space between 0,5 and %	
59	Pg 83	30	Head		Typographical error; add a space between and and schedule	**[ANDSCHEDULE] <u>AND SCHEDULE</u>**
60	Pg 86	34			Positive comment – welcome inclusion of GCP	
61	Pg 86	34	2		Typographical error	(2) An application referred to in subregulation (1) shall be accompanied by a prescribed fee contain**<u>ing</u>** at least the following information:
62	Pg 87	34	2	k	Typographical error	(k) any other information as **[many] <u>may</u>** be required by the Authority;

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63	Pg 87	34	6	a & b	Requirements of a and b may result in duplication The updated 2.11_ADR_Reporting_May 03_v1_2.doc (Reporting Adverse Drug Reactions in South Africa) is pending. The current guideline states the following should be submitted with the six-monthly progress reports: • All foreign SUSARs with the same medicine • All SAE's worldwide • Non Serious Adverse Events The Safety Reporting during Clinical Trials – Aug 2016 is pending finalisation. See pg 7 point 4 and page 13 point c. Consideration to be given to changing the Clinical Trial • Submitting the DSUR and the Line Listings, along with the 6-monthly progress reports, there will be duplication in information (SUSAR's and SAE's will be reported twice) but may be on different schedules. • Clarity on when will one be required to submit the DSUR i.e. the schedule, starting from what point (e.g. annually according to the company schedule) and if a company produces two DSURs a year, should these be submitted twice a year or together only once a year? Clarity on whether the DSUR should be unblinded or blinded? 6-monthly progress report AND annual DSUR required. Reporting will be duplicated in Progress Report Line Listings.	

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64		34	6	a	"progress reports to the Authority every six months from the date of approval of an application and 30 days after the **completion** or termination of the clinical trial; and" Confirm what is considered as Completion of the clinical trial. Is this at site level i.e. 30 days after each site is closed, at country level i.e. 30 days after all sites in South Africa are closed or Global level 30 days after the last site globally is closed?	
65	Pg 87	34			Typographical: Numbering jumps from 2 to 4; there is no number 3 included	
66	Pg 87	34	7	a & b	PI (not the sponsor) should inform the Authority of any suspected adverse events (does not specify serious or causality or expectedness) or safety concerns When the Sponsor is the applicant then the PI shall inform the HA via the Sponsor? Please confirm there is no requirement for the PI to inform the HA directly of any Adverse Events or Safety concerns.	The principal investigator **or Sponsor by delegation** shall inform the Authority of any
67	Pg 88	34	9	c	"person to whom the medicine is to be administered.." This has the potential to infringe on patient confidentiality	(c) **[person] subject number** to whom the medicine is to be administered or in the case of animals the name of the person under whose supervision it is to be administered;
68	Pg 88	34	9	g	Reference number – seek clarity on what this number is referring to, and if this is the MCC trial number – request that the trial number is not included as clinical trials supply packs are managed globally for all sites and not country specific supply packs	**[reference number]**
69	Pg 88	34A			Positive comment - Inclusion of this section is welcome,	

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					guideline required	
70	Pg 88	34A	2	a	Change from duly completed application form obtained from the CEO	duly completed application form obtained from the **[Chief Executive Officer]** **Authority**
71	Pg 88	34A	2	e	Typographical: There are Two 34A (2) e's	Renumber to end with h
72	Pg 89	34A	6		Reference 8 (4)(c) incorrect	(6) A medicine referred to in subregulation (1) shall be properly labelled and the package shall sufficiently identify the information as per the provisions of regulation **[8(4)(c)]** **8(5)(c)**
73	Pg 88	34A	9	c d f	The labels may not be big enough to include the name of the participant, site address and date dispensed Participant number and name of PI may be sufficient for identification	
74	Pg 89	35			Positive comment – welcome inclusion	
75	Pg 90	37	1	b c	Guideline required Licence Holder should advise Authority of risk minimisation & risk mitigation activities – is this a requirement for RMPs (local or core?) to be submitted? No guideline exists currently.	
76	Pg 90	37	2	a b	Positive comment – Welcome HCP responsibility herein	
77	Pg 90	37	3		Typographical – space between '36' and 'of'	
78	Pg 94	41			Refer to comments in Reg 8 (human meds)	
79	Pg 96	43	2		How are Type A amendments accommodated herein, where prior approval is not required	

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80	Pg 97	new			To follow directly after Reg 43 (3)	**X. Regulation pursuant to section 18C** **(1) The Minister of Health hereby proclaims the following Codes of Practice as binding on the marketing of medicines, medical devices and/or IVDs covered by such ~~a~~ proclaimed Codes:** **(a) The Code of Marketing Practice enforced by the Marketing Code Authority;** **(b) The Medical Device Code of Ethical Marketing and Business Practice enforced by the South African Medical Device Industry Association;** **(c) The South African Code of Marketing Ethics for veterinary Pharmaceuticals;** **(d) Any other Code and its enforcement bodies or entities *as proclaimed by the* Minister in the Government Gazette.** **(2) In order to qualify for proclamation and to create a consistent, fair and transparent system of marketing rules, a Code shall:** **(a) Be consistent with the Act and Regulations applicable to medicines, medical devices, and/or IVDs;** **(b) Aim to promote ethical, responsible and honest marketing practices;** **(c) Comprise enforcement structures operating in compliance with the principles of administrative justice;** **(d) Represent a significant number of applicants and/or holders of certificates of registration within the relevant industry of medicines,**

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						medical devices or IVDs; **(e) Be limited to matters within the scope of section 18C of the Act, and therefore exclude matters pertaining to sections 18A, 18B and 22G; and** **(f) Not contain any fundamental contradiction of any other proclaimed or to be proclaimed Codes.** **(3) Notwithstanding the membership status of the applicant / holder of a certificate of registration, the Codes proclaimed in subregulation (1) shall be binding on all applicants / holders of certificates of registration that are marketing medicines, medical devices and/or IVDs which fall within the scope of the relevant proclaimed industry Code, and such application of a proclaimed Code shall extend to the activities of any entity contracted or sanction by the applicant / holder of a certificate of registration to undertake marketing on its behalf.** **(4) Until all call-ups of medical devices and IVDs are complete, medical devices and IVDs that are deemed to be lawfully on the market, shall nonetheless be bound by a proclaimed Code and the provisions of this regulation, notwithstanding the fact that such a company may not yet be the applicant / holder of a certificate of registration.** **(5) Each proclaimed Code shall be administered and enforced by a body or entity that complies with the principles of administrative justice, and whose findings shall, subject to processes of internal appeal, be binding upon the applicant / holder of the**

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						certificate of registration. **(6) The applicant / holder of a certificate of registration shall have the right to, after the exhaustion of internal remedies set up by the applicable proclaimed Code, appeal to the Authority against a finding of a body or entity enforcing a proclaimed Code.** **(7) A body or entity enforcing a proclaimed Code may refer the applicant / holder of a certificate of registration to the Authority if such an applicant / holder of a certificate of registration:** **(a) Refuses to comply with the findings and/or sanctions imposed by the body or entity;** **(b) Has been found in contravention of a proclaimed Code on more than one occasion and appear to persist in the conduct constituting such a or a similar contravention of a proclaimed Code;** **(c) Has been found to have committed a serious breach of a proclaimed Code, which breach places the safety of the public or patients at risk, undermines the correct use- and/or leads to inaccuracies relating to the performance of efficacy of the medicine, medical device or IVD.** **(8) The Authority shall be empowered to:** **(a) Confirm, vary or reject the finding and/or sanction of the relevant body or entity; and/or** **(b) Declare the applicant / holder of the certificate of registration in non-compliance with regulation 43(3); and/or** **(c) Suspend a finding of non-compliance pending**

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						corrective action and/or pending non-contravention over a specific period. **(9) A finding of non-compliance under subregulation (7) and regulation 43(3) could lead to the temporary or permanent withdrawal or removal of a medicine, medical device and/or IVD from the market and/or the temporary or permanent withdrawal of a certificate of registration, or until such time as any conditions set by the Authority in relation to the marketing of the medicine, medical device or IVD is met.**
81	Pg 97	44	Head & Entire Subreg		Recommend title to change from Batch release of biological medicines to change to Vaccines, as it applies to vaccines and not all biological medicines If the request to change the title is not accepted, then deletion of (1) and (3). Recommend this level of detail feature in the appropriate Guideline and not in the Regulations.	BATCH RELEASE OF **[BIOLOGICAL MEDICINES]** **VACCINES** **[(1) The Authority may, with regard to the registration of biological medicines, require, in terms of section 15(7) of the Act, that at least six samples of every batch, together with six copies of the protocols of testing of the bulk batch and filling batch and one copy of the certificate of release [issued by the competent Authority in the country in which the product was manufactured], be submitted to the Authority as a batch release condition and the holder of the certificate of registration must pay the prescribed batch release fee.]** (2) The Authority may, with regard to the registration of **[biological medicines]** **vaccines**, require, in terms of section 15(7) of the Act, that at least **six samples** of every batch, together with **[six copies] one copy** of the protocols of testing of the bulk batch and filling batch of the biological medicine **[manufactured in the Republic]** be submitted to the National Control Laboratory of the Authority as a batch release condition and the holder of the certificate of registration must

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						pay the prescribed batch release fee. **[(3) The Authority may with regard to the sale of unregistered biological medicines as per the provisions of section 21 of the Act request a batch release of the medicine as per the requirements of sub regulation 1.]**
82	Pg 100	Annex 1			Annexure 1 should be reviewed to remove reference to various Medical Devices and IVDs e.g. 28 Contrast media, 29 Diagnostic agents, 32.5 Artificial tear and contact lens solutions, 32.9 Intra-uterine devices etc. as well as reference to Complementary medicines which would be covered under separate applicable Regulations i.e. for Medical Devices and for CAMs Consider using WHO ATC classification	**[28 Contrast media, 29 Diagnostic agents, 32.5 Artificial tear and contact lens solutions, 32.9 Intra-uterine devices]** **[40 Complementary medicines not otherwise specified]**
83	Pg 116	Annex 3			The detail on the updated certificate replacing the previous version is no longer reflected here. This is important for tracking and version control and therefore should be retained.	7. Name**s** and address**es** of the manufacturer**s** and the manufacturing facilit**ies** 8. Name**s** of the final product release control 10. **Original** [D]**d**ate of registration 'Add: 'This certificate replaces the one issued on….'